Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

National Drugs and Poisons Schedule Committee

Record of Reasons

50th Meeting
26-28 June 2007

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GLOSSARY

ABBREVIATION	*NAME*
AAN	Australian Approved Name
AC	Active Constituent
ACSPA	Australian Consumer and Specialty Products Association
ADEC	Australian Drug Evaluation Committee
ADI	Acceptable Daily Intake
ADRAC	Adverse Drug Reactions Advisory Committee
AGRD	Australian Guidelines for the Registration of Drugs
AHMAC	Australian Health Ministers' Advisory Council
APMF	Australian Paint Manufacturers Federation
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute Reference Dose
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods
BAN	British Approved Name
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee
CMI	Consumer Medicine Information
COAG	Councils Of Australian Governments

CPAS	Chemical Product Assessment Section
CRC	Child-Resistant Closure
CRIH	Chemical Review and International Harmonisation
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
DAP	Drafting Advisory Panel
DSEB	Drug Safety and Evaluation Branch
EAGAR	Expert Advisory Group on Antimicrobial Resistance
ECRP	Existing Chemicals Review Program
EPA	Environment Protection Authority
ERMA	Environmental Risk Management Authority
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (US)
FOI	Freedom of Information
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System for Classification and Labelling of Chemicals.
GIT	Gastro-intestinal tract
GP	General Practitioner
HCN	Health Communication Network
INN	International Non-proprietary Name
ISO	International Standards Organization
JETACAR	Joint Expert Advisory Committee on Antibiotic Resistance

LC_{50}	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD_{50}	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight
MCC	Medicines Classification Committee
MEC	Medicines Evaluation Committee
MOH	Ministry of Health (NZ)
NCCTG	National Coordinating Committee of Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOEL	No Observable Effect Level
NOHSC	National Occupational Health & Safety Commission
NPMB	Non-Prescription Medicines Branch
NZ	New Zealand
OCM	Office of Complementary Medicines
OCS	Office of Chemical Safety
ODBT	Office of Devices, Blood and Tissues
OOS	Out of Session
OTC	Over the Counter
PACIA	Plastics And Chemicals Industries Association
PAR	Prescription Animal Remedy
PBAC	Pharmaceutical Benefits Advisory Committee

PEC	Priority Existing Chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PSA	Pharmaceutical Society of Australia
RFI	Restricted Flow Insert
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SVT	First aid for the solvent prevails
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration
TGC	Therapeutic Goods Committee
TGO	Therapeutic Goods Order
TTHWP	Trans-Tasman Harmonisation Working Party
TTMRA	Trans-Tasman Mutual Recognition Agreement
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WP	Working Party
WS	Warning statement

1. PRELIMINARY MATTERS

1.7 PROCEDURAL MATTERS

1.7.1 OPERATIONS/POLICIES OF THE COMMITTEE

1.7.1.1 DRAFT TEMPLATE FOR SCHEDULING/RESCHEDULING

PURPOSE

The Committee considered endorsing a template for scheduling or rescheduling applications.

BACKGROUND

The February 2006 NDPSC Meeting agreed to develop a template to facilitate the scheduling/rescheduling process. The June 2006 NDPSC Meeting considered an early draft and agreed to foreshadow adoption of a template, posting a draft on the NDPSC website for comment. The October 2006 NDPSC Meeting considered stakeholder feedback and agreed:

- That the template, as amended, provided suitable guidance to industry and would improve the efficiency with which the Committee could consider applications.
- To post the template on the NDPSC website including a request that those making a submission to the June 2007 NDPSC Meeting consider voluntary use of the template.
- To advise NCCTG of the February 2007 consideration of the proposed template.
- To amend the NDPSC guidelines to allow electronic submission as an alternative to the mandatory submission of 25 hard copies of an application. These amendments were forwarded to the November 2006 NCCTG Meeting for consideration.

The February 2007 NDPSC Meeting:

- Noted NCCTG endorsement of the draft template (including a June 2007 voluntary trial) and of amendments to the NDPSC guidelines to allow electronic submissions. Members noted that these amendments had been incorporated into the NDPSC guidelines.
- Agreed to consider finalising the template at the June 2007 NDPCS Meeting, noting that the template would always be open for comments and improvements.

DISCUSSION

Members were advised that the only submission received for the June 2007 NDPSC Meeting which utilised the template had been withdrawn.

Members recalled the following previous considerations:

The October 2006 NDPSC Meeting:

- Confirmed that the template was intended for scheduling or rescheduling applications made directly to the Committee i.e. not for those coming via a regulatory agency. It was also confirmed that the template was not intended to be used for general communications from stakeholders such as pre– and post–meeting comments.
- Agreed to include reference to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) template for presenting toxicology data which may assist some stakeholders.
- A Member asserted that specific guidance would become possible following the proposed splitting of the NDPSC into medicines and chemicals committees as the focus of these new committees would be different. The Members noted, however, that a template would currently need to remain generic because of the nature of the different types of submissions currently considered by the Committee.
- Was advised that XXXXX welcomed the discussion and supported the Committee's moves to trial the template, noting that there was going to be a template under ANZTPA and that the NDPSC template would allow a form to evolve that was acceptable to everyone.

The February 2007 NDPSC Meeting:

- Agreed that while a "final" template could be endorsed at the June 2007 NDPSC Meeting, it would still be open for comments/improvements, particularly given the wide range of applicants. A Member supported giving the Secretariat the flexibility to maintain the template, advocating that only major template changes should be expected to come through to the Committee for consideration.
- A Member noted that although industry should be strongly encouraged to use the template, it could not be mandated as this may not allow equitable access by a range of stakeholders. The Committee confirmed this position, but would be seeking an industry commitment to electronic submissions using the template.
- Noted that NICNAS successfully encouraged uptake of its electronic template by making electronic submissions cheaper than hardcopy. Members noted that this may be worth pursuing in the future should the Committee move to a cost-recovery model as expected.
- A Member asserted that it would be worth having an industry training day regarding the template. Members noted subsequent discussion between the XXXXX agreed that it would be more productive if ASMI liaised with industry to locate organisations that would be willing to use the template to make their next submission. The Secretariat would be available to offer advice on using the template. Any lessons learnt could then help refine the template/guidance notes. In addition, if necessary, the Secretariat could supply "case studies" to address any common issues encountered

by industry (which could be included in one of ASMI's newsletters). Members noted that ASMI recently included a notice in its newsletter advising that a template for electronic submissions was available on the NDPSC website.

Members noted the following points from XXXXX pre–meeting comment (noting that XXXXX had not had the opportunity to use the template yet):

- The template appeared more prescriptive than the current NDPSC Guidelines. Much of the criteria that are required to be addressed need to be as extensive as the data allow and no criteria are to be deleted or left blank. The Guidelines, however, state that the assessment factors are a guide only and not an inflexible standard from which there is no deviation. This means there is a conflict between what the Guidelines require and what the Template requires. Members recalled that there was a deliberate tightening of the language around addressing criteria for scheduling as a result of Members input while developing the template – noting some stakeholder comments at previous Meetings supported the increased clarity of the criteria wording. The NDPSC Guidelines, however, have not yet been updated to reflect this tightening – this would have been inappropriate while the template was still a draft. Members also noted that the template criteria are not as inflexible as XXXXX asserted, and that criteria need not be addressed – as long as this can be justified by the applicant.
- There seems to be some duplication between Parts A, B & C. While this template will be used for both drugs and poisons in the short term, ultimately the information required for pharmaceuticals should differ from that required for poisons. For example, where substances are to be rescheduled much of the information has already been evaluated and approved to the TGA – it is questionable why this needs to be restated for the Committee. XXXXX suggested that perhaps a 'justification' for not including some of the criteria might be that the TGA has already assessed that aspect of the substance. Members noted that substances which are not evaluated by TGA (those not for human therapeutic use) were not addressed by this comment. Members recalled that the template needed to remain generic as discussed above. It was also noted that the argument of not providing safety data because it had gone to TGA did not reflect the current practices of the Committee. In addition the Committee uses such data for a different purpose – scheduling of a substance.
- In commenting on the overview section in Part A of the template, it was noted that much of this may be repeated in Part B and it might be preferable to require this section to be in dot point format to ensure conciseness. It was also asserted that the requirement for a 'critical evaluation of the schedule in light of the scheduling factors' was confusing and was presumably a summary of the criteria?
- Suggested an addition to criteria D under Part B "include current patterns of use locally and overseas if applicable". Members supported this as an appropriate addition to the template.

- It is noted that electronic copies of references should be included with the submission. This was asserted to infringe copyright as many papers are not permitted to be sent electronically but can be used in hard copy form for 'scientific purposes'.

Member's recalled that following discussion of copyright concerns the February 2007 NDPSC Meeting agreed that it did not appear to be an issue. It was noted that references had always been a component of NDPSC applications (and indeed for the many applications made to regulators such as TGA and APVMA) and did not see that moving from hard–copy to electronic would make any difference. The Committee confirmed that it did not intend to distribute these references.

Member's also noted the information sheet from the Australian Copyright Council's Online Information Centre (http://www.copyright.org.au/) regarding the use of copyright material for the services of the Commonwealth or a State. This site advised that the Copyright Act does not provide any guidance on the meaning of "for the services of the Commonwealth or a State". However, it seems that not every use of copyright material by a government can be made under section 183; only those dealings with copyright material which are governmental in nature and where there is some element of public interest involved are likely to be covered by section 183. Members noted that this website's advice was of a general nature, and that specific legal advice should be obtained.

Members also noted that the copyright issue would be relevant to the various TGA Committees moving to an e-agenda process. It was noted that the copyright issue had not been considered by XXXXX which also uses an e-agenda.

OUTCOME

The Committee agreed:

- To adopt the draft template (as amended at the June 2007 NDPSC Meeting) for use by applicants making Scheduling or Rescheduling submissions (will be made available at http://www.tga.gov.au/ndpsc).
- To refer the issue of copyright on references included in electronic applications to expert Committees such as NDPSC to XXXXX for advice and clarification.

1.7.1.2 [ITEM DELETED]

1.7.1.3 POLICY FOR REFERENCING ENANTIOMERS

PURPOSE

The Committee considered the need for a policy when referencing enantiomers in schedule entries.

BACKGROUND

Part 1 – 'Interpretation' currently advises that:

1. (2) Unless the contrary intention appears a reference to a substance in a schedule or an appendix to this Standard includes:

(e) except where the substance is levomethorphan or levorphanol, every stereoisomer of the substance and every salt of such a stereoisomer; and

[No discussion was located as to why the exceptions for levomethorphan and levorphanol were set out in 1.(2)(e) rather than in the specific Schedule entries for these compounds.]

The October 2006 NDPSC Meeting the considered the scheduling of dichlorprop-P. It was noted that the proposed use pattern made use of the single R–(+) stereoisomer of dichlorprop (termed dichlorprop–P). Due to the toxicology profile, including potential to cause severe eye irritancy, it was recommended that the Committee consider an entry for "Dichlorprop–P (the R–enantiomer)" in Schedule 6. The Committee noted, however, that the potential for severe eye irritancy was a risk from both enantiomers of dichlorprop and therefore agreed to include "includes the R and S enantiomers" in the Schedule 6 entry.

The February 2007 NDPSC Meeting confirmed the above decision, with a minor editorial change ('including' to replace 'includes'). A Member questioned the need to include reference to the R– and S– enantiomers in the SUSDP schedule entry given Part 1.(2)(e). The Committee requested the Secretariat to investigate why a specific reference to the R and S enantiomers for 2,4–dichlorprop had been listed in the SUSDP, and if necessary, develop for consideration a policy against which enantiomers could be considered in future.

DISCUSSION

Members noted that in addition to 2,4–dichlorprop the only other entries to reference enantiomers were for indoxacarb. Members recalled the following from the considerations of indoxacarb:

- The ISO approved name "indoxacarb" applies only to the insecticidally active S–enantiomer (also known as DPX-KN128). The R–enantiomer (DPX-KN127), while not insecticidally active, has mammalian toxicity like the S–enantiomer. The R– and S– enantiomers could be regarded as ~ equivalent in terms of mammalian toxicity.
- XXXXX therefore recommended, and the Committee agreed, that the indoxacarb entry should cover both the R– and S–isomers.

Members noted that the reference to R– and S– enantiomers for indoxacarb and dichlorprop–P appeared to have been based on providing clarity to stakeholders, as 1.(2)(e) would already capture all enantiomers. Without this clarity there was the possibility that stakeholders would think that the entries only applied to the insecticidally active enantiomers. This would not have been an appropriate conclusion as both enantiomers for these compounds posed a risk to human health (demonstrated mammalian toxicity for indoxacarb, and eye irritancy for dichlorprop–P).

OUTCOME

The Committee:

- Confirmed that a substance parent entry captures all stereoisomers (which includes all enantiomers) of that substance by application of Part 1.(2)(e).
- Agreed, however, that reference to enantiomers in an entry may remain appropriate where this will provide clarity, as was the case for indoxacarb and dichlorprop–P.
- Agreed that the exception to Part 1.(2)(e) for levomethorphan or levorphanol would be better expressed by including the contrary intention in the schedule entry. Members therefore agreed to foreshadow amendments to the levomethorphan and levorphanol entries, with a consequential amendment to Part 1.(2)(e).

FORESHADOWED DECISION (for consideration at the October 2007 Meeting)

Part 1 – Interpretation – Amendment

Amend paragraph **1.**(2)(e) to read:

1. (2) Unless the contrary intention appears a reference to a substance in a schedule or an appendix to this Standard includes:

(e) every stereoisomer of the substance and every salt of such a stereoisomer; and

Schedule 8 – Amendment

LEVORPHANOL – amend entry to read:

LEVORPHANOL (excluding its stereoisomers).

Schedule 9 – Amendment

LEVOMETHORPHAN – amend entry to read:

LEVOMETHORPHAN (excluding its stereoisomers).

1.7.1.4 [ITEM DELETED]

1.7.1.5 [ITEM DELETED]

1.8 NDPSC WORKING PARTIES

1.8.1 TRANS-TASMAN HARMONISATION WORKING PARTY

1.8.1.1 CADMIUM COMPOUNDS AND CADMIUM SULPHIDE

PURPOSE

The Committee considered the scheduling of cadmium compounds including cadmium sulphide.

BACKGROUND

The February 1970 PSC Meeting agreed to include preparations containing ≤ 2.5% of cadmium sulphide for human therapeutic use in Schedule 5. Members also agreed to include a parent entry for all other cadmium salts and compounds in Schedule 6 due to toxicity.

The February 1988 DPSSC Meeting noted that animal studies had shown an association between cadmium exposure and a variety of tumours. Human epidemiological studies indicated an increase in lung cancers as a result of occupational exposure to cadmium. Cadmium is acutely toxic at low doses and in animal tests cadmium produced embryotoxicity, foetotoxicity and teratogenicity. The major use in Australia at the time was in the electroplating industry and other industrial products and applications. The Meeting agreed to maintain the Schedule 6 entry and to request that no domestic agvet products be registered. This decision was confirmed by the May 1988 DPSSC Meeting.

The August 2000 NDPSC Meeting considered consistency between schedule entries and Appendix I "Uniform Paint Standard". The Committee agreed to an exemption from the Schedule 6 cadmium compounds entry for paints and tinters containing ≤ 0.1% cadmium.

The February 2007 NDPSC Meeting considered the unharmonised status of cadmium sulfide for human therapeutic use and agreed to foreshadow consideration of cadmium compounds, including cadmium sulfide, for human therapeutic use at the June 2007 NDPSC Meeting.

DISCUSSION

Members noted the following from a Secretariat's review of possible human therapeutic use patterns of cadmium compounds:

- A search of Martindale revealed no cadmium therapeutic uses apart from:

- Cadmium sulfide – used topically in some countries for the treatment of skin and scalp conditions.
- Cadmium sulfate – used for the treatment of eye irritation.

- The above cadmium salts had also been used in homoeopathic preparations.
- The Secretariat was unable to locate any other therapeutic uses of cadmium compounds.

A pre-meeting comment from XXXXX included the following points:

- Noted that the pre-meeting gazette notice referenced item 1.8.1.3.2 of the Record of Reasons from the February 2007 NDPSC meeting. However, no such item appeared in the Record of Reasons. The Secretariat confirmed that 1.8.1.3.2 was inadvertently omitted from the February 2007 Record of Reasons and that this had been corrected.
- As item 20.1 in the Record of Reasons noted a proposal to amend the spelling of cadmium sulphide to cadmium sulfide, XXXXX assumed that this was the item for consideration, in which case XXXXX supported the amendment. However, XXXXX reserved the right to provide post–meeting comment if the details of this agenda item were different from the above.

Members recalled the following from the February 2007 NDPSC Meeting:

- An ARTG search located only 1 product containing cadmium sulfide (and no products containing cadmium). Cadmium sulfide, 0.044%, was listed as an excipient in a medical device – a dentine adhesive. This device appeared to qualify for the Appendix A general exemption for medical and veterinary adhesives, glues and cements. Members noted that medical devices not required to be on the ARTG would not have been located by this search.
- The Micromedex entry for cadmium sulfide provided the following:
  - Cadmium sulfide is a dermatological agent and antiseborrheic.
  - Cadmium sulfide releases hydrogen sulfide upon contact with water or acids.
  - Cadmium sulfide is used in photoconductors, dandruff shampoos, pigments and phosphors, electronic components, and in solar cells.

  <u>Acute clinical effects</u>:

  - No studies were found for acute exposure to cadmium sulfide in humans. It was not acutely toxic in experimental animals (RTECS), and was generally regarded as being less toxic than more soluble cadmium compounds.
  - Acute inhalation of cadmium and its salts can cause pulmonary oedema; fatal in approximately 20% of cases. Ingestion of cadmium or its salts produces immediate gastrointestinal distress with pain, nausea, vomiting, diarrhoea,

excessive salivation, muscular cramps, and signs of CNS depression (such as dizziness, weakness, headache, cardiovascular collapse, and shock), and death.

Chronic clinical effects:

- Cadmium sulfide is relatively inert for causing lung damage in chronic inhalation exposure. Some cases of emphysema have been reported, but only after at least 25 years of exposure. Kidney injury with proteinuria has developed following chronic exposure to cadmium sulfide.
- In a 30–day rat inhalation study, cadmium sulfide was absorbed only one–tenth as much as cadmium chloride or cadmium oxide.
- If cadmium sulfide is being used under conditions where cadmium fumes may be generated, inhalation exposure might cause metal fume fever, a flu–like condition involving fever, chills, sweating, aches and pains, and difficulty breathing. Symptoms of metal fume fever generally appear within hours of exposure and subside within 24 to 48 hours, leaving no permanent effects.
- IARC (2004) listed cadmium sulfide as carcinogenic to humans (rating 1). In animal studies, cadmium sulfide was carcinogenic in rats. It is relatively insoluble; tumours developed at the site of injection. Cadmium sulfide caused broken chromosomes in cultured human cells and also caused in vitro transformation of hamster cells.
- Cadmium caused birth defects in several species of laboratory animals and was embryotoxic and fetotoxic. There was some evidence that cadmium may be a human reproductive hazard. There had been isolated cases of impotence and microscopic changes in the testes of men working with cadmium.

- Members were advised that cadmium was not currently listed in the *Required Advisory Statements for Medicines Labels* (RASML).
- The Members generally agreed that cadmium sulfide for human therapeutic use should be removed from Schedule 5. Noting the toxicity of cadmium compounds the Committee discussed whether to include a parent entry in Schedule 4 for human therapeutic use (with an exemption to allow excipient use of cadmium sulfide below 0.1% which appeared to present little risk).
- The Committee noted that while cadmium sulphide had been gazetted for the February 2007 Meeting, cadmium compounds had not, so any decision for cadmium compounds would need to be foreshadowed. Additionally, a Member noted that a list of possible human therapeutic use patterns for cadmium compounds would aid in considering the scheduling of these substances. The Committee therefore agreed to foreshadow the scheduling of cadmium compounds for human therapeutic use at the June 2007 NDPSC Meeting.

- It was also noted that sulfide is traditionally spelled 'sulphide' in British english, but IUPAC has adopted the spelling "sulphide", as has the Royal Society of Chemistry Nomenclature Committee.

Members also note a 2002 Queensland Health public notice on cadmium (http://www.health.qld.gov.au/phs/Documents/ehu/2665.pdf) which included a summary of Australian exposure to cadmium.

The Committee generally agreed that there were strong concerns about allowing any cadmium compound for therapeutic use, especially given its propensity to bioaccumulate. A Member proposed that there should therefore be no exemption and that the following Schedule 4 entry be considered:

CADMIUM for human therapeutic use.

Other Members indicated that a Schedule 4 entry did not sufficiently restrict cadmium from use in human therapeutics, and instead proposed an Appendix C listing based on concern about cumulative renal effects. A Member noted that there may also be a need to amend the various exemptions in Appendix A so as not to apply to those human therapeutics containing cadmium. An alternative suggestion was to reflect the 1988 request to APVMA (that no domestic agvet products containing cadmium be registered) and write to TGA requesting that no cadmium containing human therapeutic be registered.

The Committee noted that banning cadmium from human therapeutic use may not have been foreseen as a possible outcome by sponsors and that it was therefore appropriate to defer consideration until the October 2007 NDPSC Meeting to allow an additional opportunity for public comment.

OUTCOME

The Committee agreed to defer consideration of the scheduling of cadmium (including cadmium sulfide) when for human therapeutic use to the October 2007 NDPSC Meeting.

1.8.1.2 STIMULANT LAXATIVES

PURPOSE

The Committee considered Trans–Tasman Harmonisation Working Party (TTHWP) recommendations for harmonisation for stimulant laxatives deferred from the June 2006 and February 2007 NDPSC Meetings.

BACKGROUND

At the June 2006 NDPSC Meeting the Committee agreed that consideration of stimulant laxatives would need to be deferred to a future meeting to allow a more thorough risk and regulatory impact assessment.

The October 2006 TTHWP meeting endorsed the recommendations and actions in relation to each medicine listed in Table 3 "Deferred harmonisation proposals" from the June 2006 NDPSC Meeting, including actions for stimulant laxatives. The Secretariat arranged to seek advice from XXXXX on these issues.

The scheduling of stimulant laxatives was considered by the Committee at the February 2007 NDPSC Meeting. Advice was received from XXXXX but not XXXXX. However, the Committee agreed to further defer consideration of the scheduling of stimulant laxatives to the June 2007 NDPSC Meeting in order to allow additional advice to be sought from relevant expert bodies such as XXXXX

DISCUSSION

Members recalled the following from the February 2007 NDPSC Meeting:

- Advice from XXXXX was also received regarding the hydroxyanthracene derivative laxatives (aloin, aloes for internal use and sennosides) which stated that there was no need for increased regulation of these substances.
- XXXXX stated that they were unable to comment regarding the scheduling of sodium picosulfate and bisacodyl as they would need to seek the advice of XXXXX first.
- It was agreed that the Committee would have to obtain further information from XXXXX and relevant expert bodies such as XXXXX before it could make a properly informed scheduling decision for these substances.

Advice Sought

At the February 2007 NDPSC Meeting it was felt that, before a decision on scheduling of stimulant laxative substances could be made, advice should be sought from the professional bodies which deal with eating disorders and gastrointestinal disorders, XXXXX. It was felt that, as these are the professional bodies representing the practitioners who deal with patients using laxatives on a regular basis, they would be able to provide real world information about the use and misuse of these substances.

XXXXX provided a pre–Meeting comment in which XXXXX stated that there was no compelling reason, XXXXX, to recommend the rescheduling of stimulant laxative agents. XXXXX stated that the management of eating disorders is multi–faceted and, while the abuse of laxatives can be a symptom of the overall disorder, it was not the essence of the disorder, nor was it always involved in the disorder. XXXXX noted that

there may be some value to a small number of patients if stimulant laxatives were available as Schedule 2 medicines as it may allow pharmacists to identify them as having an eating disorder. However, most people with an eating disorder would not be identifiable and they may only interact with non−pharmacist staff. XXXXX further noted that it would also be possible for such patients to purchase large supplies of laxatives by shopping at multiple other pharmacies. Thus, XXXXX felt that there was no reason to reschedule stimulant laxatives to Pharmacy Only substances as it would not achieve any real benefit to patients with eating disorders.

A late submission was received from XXXXX. The Committee decided to consider this submission and made note of the following. XXXXX stated that XXXXX saw no problem with the proposal to include stimulant laxative agents in Schedule 2. However, XXXXX also stated that as many of these substances were sold in complementary and traditional Chinese medicine products, the Committee would need to consider these situations for consistency.

Pre-Meeting submissions

A request for further input, particularly regarding the scheduling of sodium picosulfate and bisacodyl, was sent to XXXXX. A response was received from XXXXX stating that the consideration of this matter would have to be taken to XXXXX and that XXXXX would prepare an assessment of this issue for XXXXX consideration. However, XXXXX stated that XXXXX that the matter could be considered at was 7 June 2007.

Informal advice was received from XXXXX stating that XXXXX did not feel that there was sufficient evidence that scheduling bisacodyl and sodium picosulfate would prevent potential abuse of products containing these substances. A copy of the paper that went to XXXXX was also provided.

The Committee noted that there had been brief reports in the media about the incidence of laxative abuse increasing. This had been reported as part of a wider report on an overall increase in the incidence of all eating disorders. The studies mentioned were small but the information did support other empirical evidence.

XXXXX provided a pre−Meeting comment which stated that XXXXX had no issue with stimulant laxatives becoming scheduled substances given the abuse of laxatives by patients with eating disorders was well reported. XXXXX also stated that they presumed that this would mean that such products would become registered medicines and thus require evaluation of safety and efficacy. XXXXX provided submissions supporting this.

XXXXX provided a submission in which XXXXX opposed the scheduling of stimulant laxatives and requested that comprehensive expert advice was sought on the matter prior to a decision being made. XXXXX reiterated the points made in XXXXX submission to the February 2007 NDPSC Meeting on this matter.

XXXXX provided a pre-Meeting submission in which the upscheduling of stimulant laxatives was opposed. XXXXX manufactures the product XXXXX (which contains sennosides). XXXXX felt that the up scheduling would serve to disadvantage consumers by restricting their access to XXXXX, which have been available at the general sale level for a lengthy period of time. XXXXX stated that XXXXX had not received any reports of abuse or misuse of the product in its 100 year history and the ADRAC database had received no reports from 1995 to the present (period of time surveyed). XXXXX noted that the sales of this product had not increased in the past nine years and the market for stimulant laxatives in supermarkets was in slight decline. XXXXX stated that this suggested that there had been no increase in the abuse or misuse of XXXXX product. XXXXX also stated that XXXXX products are targeted to older consumers and that it was emphasised that the product was not meant for long–term use.

XXXXX provided a pre–Meeting submission which did not support any changes to the current scheduling of stimulant laxative agents. XXXXX stated that there was no substantial evidence to suggest broad abuse, dependency or long term damage through use of these substances. XXXXX stated that it was not common for stimulant laxatives to be the primary driver in patients with eating disorders and such disorders are complex and require medical management. XXXXX noted that the CMEC had advised, with regards to hydroxyanthracene derivative laxatives, that there was no need for any change to regulatory requirements. XXXXX recommended that any concerns regarding laxative use would be better addressed by educating healthcare providers about the potential abuse by those patients suffering eating disorders.

XXXXX provided a pre–Meeting submission which did not support any change to the scheduling of the stimulant laxatives listed. XXXXX main points were:

- There are a number of Australian studies (Mond JM *Behav Res Ther.* 2006 Jan, **44**(1):53–62; and Abraham *MJA* 2003 Jun, **178**(16):606–611) showing that laxative use ranked lowly when compared to other behaviours characteristic of eating disorders. Mond et al surveyed 5255 ACT women on eating disorder behaviours and found that laxative abuse was highest in the 23–27 and 38–42 age range with 2.1% of subjects reporting misuse and a total of 1% of subjects reporting regular misuse. Non-laxative diet pill use was seen in approximately 3% of patients, hard exercise in approximately 30% and bulimic episodes recorded at approximately 20% of patients. Abraham surveyed 438 female students and found that 2% of these had abused laxatives in the previous 28 days. However, Abraham also surveyed a subset (n=116) of subjects with eating disorders and found 18% of these patients misused laxatives. It was also found that 20% of these patients used smoking, 30% engaged in self-induced vomiting, 83% restricted food intake, 24% exercised excessively and 23% drank coffee as methods of weight control.
- A US study by Tozzi et al (*Psychosom Med.* 2006 May–Jun, **68**(3):470–7) of 1021 patients with eating disorders which found that 7% of patients used laxatives as their

only purging activity and 55% used it in combination with other methods. Tozzi stated that laxative abuse was associated with worse eating disorder and that the function of it may differ across individuals with eating disorders, alternatively serving as a method of purging and a form of self–harm.

- XXXXX stated that patients with eating disorders engage in a multiplicity of behaviours, not all of which are the same type or degree and this data shows that misuse of laxatives was not a first line behaviour engaged in by such patients. XXXXX further stated that the restriction of access to laxatives will not cause change in eating disorder behaviours and would only serve to inconvenience those responsible users.
- XXXXX also addressed the concern of the Committee about long-term use and dependency on the substances. XXXXX cited a study by Wald (*J Clin Gastroenterol.* 2003 May-Jun, **36**(5):386-9) which looked at two different categories of laxatives (diphenylmethanes and anthroquinones) and what effect these may have on colonic nerve and smooth muscle function. The study concluded that although structural damage is caused to epithelial cells, the damage is reversible and its clinical significance is unproven. It was also concluded that there was no evidence that chronic use of stimulant laxatives causes structural or functional impairment of the colon.
- Reference was made to the principles of Trans-Tasman harmonisation, particularly the point about harmonising to the least restrictive schedule while giving due consideration to public health issues. Reference was also made to the Minutes of the 60th CMEC Meeting and the fact that CMEC recommended to NDPSC that no scheduling change be made to hydroxyanthracene laxatives.
- Based on the above evidence XXXXX concluded that restricting access to stimulant laxatives on the basis of potential for misuse is not a quality use of medicines based solution as it failed to recognise the complexity of eating disorder behaviours. It was further stated that there was no current scientific evidence to warrant a change of scheduling on safety grounds. XXXXX stated that the MCC should be challenged to produce the evidence that pharmacy restriction of stimulant laxatives had produced health outcomes significantly better than Australia with relation to rates of laxative misuse amongst the general population and amongst patients with specific eating disorders.

XXXXX provided a substantial pre-Meeting submission relating to the scheduling of bisacodyl and sodium picosulfate. XXXXX opposed any change to the scheduling of these agents. The Committee noted the following points:

- Reference was made to the principles of Trans-Tasman harmonisation, particularly the principle of adopting the least restrictive scheduling for a substance.
- The issue of laxative abuse by patients with eating disorders was discussed. XXXXX accepted that any laxative agent may be abused by a small number of patients,

including young women with eating disorders, however restricting access to bisacodyl and sodium picosulfate by legitimate consumers would not necessarily reduce the number of individuals suffering such disorders. XXXXX cited the Mond et al study which was cited by XXXXX. XXXXX also quoted a Canadian study of weight loss behaviours by McVey et al (n=1458) (*Preventive Medicine* 2005, **2**(40) 1–9) of students aged between 10 and 14. This study showed the prevalence of laxative use at 1.9%. XXXXX also noted XXXXX had reviewed the report Mental Health of Young People in Australia (2000) which was referred to by the Committee in the June 2006 RoR. XXXXX stated that, while this data was valid, it should be noted that the use of laxatives was combined with vomiting, therefore there was no actual data for the prevalence of laxative abuse alone in this report.

- XXXXX noted that there were currently 24 products on the ARTG containing bisacodyl (5 export only) and 6 containing sodium picosulfate (a total of 7 of these products were sponsored by XXXXX). XXXXX noted that up-scheduling of these substances would incur significant regulatory impact. XXXXX stated, however, that if New Zealand harmonised with Australia on the scheduling of these agents, it would not result in a reduction of regulatory control of these agents and further noted that under ANZTPA all dietary supplements in New Zealand would be regulated.
- XXXXX noted that despite the unscheduled nature of these products in Australia, there were already significant regulatory controls imposed by the TGA and that this had served to eliminate the leakage of these substances into and use by inappropriate subpopulations.
- XXXXX provided data on the safety of bisacodyl and sodium picosulfate. For the period of product launch (not stated) to 27 February 2007, XXXXX stated that there had been no adverse event reports received by ADRAC for abuse of sodium picosulfate and world wide the reports of abuse show an incidence of 0.9/ 100,000 patient years in the period 1 January 2000 to 31 December 2004 (reports provided). For bisacodyl, XXXXX stated that in the period from 1960 to 27 February 2007 only one report of abuse has been received by ADRAC (report provided) and worldwide (17 January 1999 to 16 January 2004) the reports of abuse showed an incidence of 0.06/100,000 patient years (reports provided). XXXXX stated that only 4 of these reports involved young women potentially suffering from an eating disorder.
- The Committees' concern about long-term use of stimulant laxatives was addressed. XXXXX stated that data-mining from the company's global drug database and safety assessments of cases of misuse/ abuse and overdose had shown that, even at long-term administration of high doses, sodium picosulfate and bisacodyl had a low incidence of adverse events. Further, XXXXX stated there was no evidence of tolerance, withdrawal or physical dependency with these substances and quoted a number of references to this effect.
- XXXXX stated that the appropriate labelling of these products had reduced the likelihood of inappropriate use of them. The CMI is contained in the packages for XXXXX products and contains warnings regarding long-term use, the indications and

dosage for the product, precautions and information on overdose. XXXXX also noted that the primary packaging of the product contains clear warnings against long-term use.

- XXXXX believed that all the above information clearly showed that any problem that might exist regarding the misuse and abuse of laxatives is not an issue with sodium picosulfate and bisacodyl. Thus, XXXXX believed that these substances should remain unscheduled.

A search of PubMed revealed a number of studies (Bryant-Waugh *Int J Eat Disord.* 2006 Jul, **39**(5):404-9; and Turner *J Am Acad Child Adolesc Psychiatry.* 2000 Mar, **39**(3):378-85.) relating to the prevalence of laxative abuse amongst patients with eating disorders. These studies concluded that laxative abuse is common among patients with eating disorders, with approximately 19% of adolescents and 26% of adult patients misusing them. A study (Jones *CMAJ* 2001, **165**(5):547-52) of eating disorder behaviours in teenaged girls (n=1739) found that the most common behaviours were dieting (23%), binge-eating (15%), self induced vomiting (8.2%) and use of diet pills (2.4%). By contrast laxative misuse was practiced by 1.1% of subjects. Another study by Carter (*Behav Res Ther.* 2001 May, **39**(5):625-32) similarly found that in young teenaged girls laxative misuse was practiced by 1% of subjects with 4% practicing self-induced vomiting and 8% regular binge eating.

A study (Motola *Adv Ther.* 2002 Sep-Oct, **19**(5):203-8) of purchasing habits of laxatives in 70 Italian community pharmacies (n=7324 patients) showed that the majority of purchasers were female with an average age of 45.9 years. It was found that a physician influenced the choice of a laxative in 37.7% of cases and a pharmacist in 20.5%, with 58.2% of patients consulting a doctor or pharmacist because of constipation. It was also determined that only 59.8% of patients used laxatives correctly. The authors concluded that long-term use of laxatives can cause serious medical consequences and that healthcare personnel should counsel patients on the proper use of these substances.

A late post-Meeting comment was received from XXXXX opposing the rescheduling of stimulant laxatives. The Committee chose to consider this comment and noted:

- XXXXX (containing bisacodyl) were sold in eight countries, six of which they were available as general sales medicines. The product had a low risk of adverse events and there was a lack of evidence for correlation between stimulant laxative use and pathological bowel changes. Also, there was a lack of studies showing that stimulant laxatives were the most commonly abused form.
- The proposed change to scheduling would unfairly target the stimulant laxative agents mentioned while not regulating other laxative products, including homeopathic agents, which may produce a stimulant effect. The Committee assumed that XXXXX may have been referring to complementary medications here. Homeopathic substances generally are a 1,000 fold (or greater) serial dilution of a mother tincture in water, ethanol, or glycerol.

- XXXXX pointed to the assertion "...unscheduled status did not give rise to safety issues from normal use" in the February 2007 NDPSC RoR and stated that, given this, it seemed that the Committees' main concern is the abuse of these substances by patients with eating disorders. XXXXX suggested that if this was indeed the case then all laxative agents, not just stimulants, should be scheduled as, if patients with eating disorders could not easily access one type, they would move on to another, more easily accessible one.
- XXXXX referred to the NDPSC guidelines for inclusion of a substance in Schedule 2 and stated that the point "counselling is available if needed" in this instance, would seem to assume that if a person with an eating disorder intended to purchase the product to abuse it, they would not be willing to seek counselling even if offered. XXXXX also made the point with regard to the "low potential for abuse and misuse" that there were a number of laxative agents on the market (diet pills and supplements) which were unscheduled and more easily abused than stimulant laxatives. The Committee was unsure exactly which products were being referred to here.
- The current labelling of the XXXXX product warned the consumer about dangers of overuse of the substance. XXXXX stated that, if warranted, a potential alternative to rescheduling may be to strengthen these warnings.
- XXXXX stated that until a direct and substantial correlation could be made between stimulant laxative abuse and safety concerns in patients with eating disorders, it would be unfair to reschedule these agents while leaving other laxative agents unscheduled.

The Committee considered the possible ramifications once the transitional period for the joint scheme ends and noted that should these substances remain unharmonised, dual licences (i.e. a single approval allowing supply in both countries) may not be possible for affected products. The regulatory impact of this may be significant.

A Member stated that the information provided by XXXXX regarding the abuse of laxative agents was very pertinent information to the Committee's consideration as one of the major concerns of the MCC and the Committee in the past had been the potential for abuse with these agents. The Member noted that while XXXXX did not oppose a scheduling change, they did not positively support one either. The Member also noted that there was little information on the XXXXX website and felt that the fact that XXXXX did not feel able to provide comment on the issue without performing a full literature review probably meant that XXXXX were not overly concerned that abuse of stimulant laxatives was a problem in the community.

A Member stated that despite extensive canvassing of relevant stakeholder groups, the Committee did not seem to have obtained concrete evidence of significant problems of abuse or adverse effects with the use of stimulant laxatives in Australia despite their long and widespread availability in the open marketplace. Another Member stated that the data produced did show evidence of harm, with approximately 1-2% of young women who

had not been identified with an eating disorder saying that they used laxatives to lose weight on a regular basis (referring to the Mond et al study discussed above). Another Member stated that the majority of these young women are likely to grow out of this behaviour without any adverse effects. A Member stated that there was a need to differentiate between the two types of laxative agents as one was subject to abuse and the other was not, thus the appropriate thing to do would be to schedule the substances which were at risk of being abused.

Another Member stated that, although the Australian study (Turner et al discussed above) showing that 32% of patients with anorexia nervosa used stimulant laxatives was conducted at an eating disorders clinic and therefore captured the worst patients, this may indicate that the usage in that particular patient population is higher than thought as there may be many patients that go undetected. Therefore the substances should be scheduled. Anther Member argued that the logical sequale to that argument was that if there was direct evidence of harm then the substances should be included in Schedule 4 where the abuse could be monitored through the provision of prescriptions. The Member stated, however, that the professional organisations who deal with these patients on a daily basis had felt that there was no strong need for these substances to be scheduled.

A Member reminded the Committee that patients with eating disorders can be difficult to detect, especially in the community where body shape is not necessarily an indicator and pharmacists may not be able to always identify them. Another Member agreed with this and cited XXXXX submission which stated that the disorder would exist whether or not the laxatives are scheduled or unscheduled and the availability of stimulant laxatives does not determine the prevalence of the disease. The Member stated that restricting access to the substances may change the behaviour of patients but it would not affect the prevalence of the disorder, as laxative availability does not cause eating disorders and that laxative abuse is one of the behavioural manifestations of the disorder. Another Member stated that patients with eating disorders who abuse laxatives are the hardest to treat, but another Member pointed out that the severity of the disease is not caused by laxative abuse, rather laxative abuse is an indicator of the severity of the disease and that this was a small subset of the eating disorder population.

A Member stated that scheduling these substances would allow patients buying these products access to professional advice if they required it and allow for potential early intervention for patients with eating disorders. A number of Members questioned whether this would actually occur given the difficulty which can be encountered in easily identifying these patients as stated in XXXXX submission and by other Members of the Committee.

A Member stated that the Committee also had to look at whether these substances were safe when they were used normally and long-term and noted that safety risks had also been a previous concern of the MCC and the Committee. The Member stated that there had been quite a lot of evidence presented to the Committee that these substances did not increase the risk of cancer, they did not cause electrolyte imbalances and they did not

induce rebound constipation, all of which had been past concerns of the Committee. The Member stated that from an appropriate use standpoint there was no evidence presented which would require the substances be rescheduled.

A Member stated that one of the underpinning principles of Trans-Tasman Harmonisation was that substances be harmonised to the lowest applicable schedule. The Member recommended that this approach should still be taken and that New Zealand be asked to reconsider harmonising on the scheduling of stimulant laxative agents in light of the new evidence presented to the Committee. The New Zealand Member stated that the MCC would be open to reconsidering the matter.

OUTCOME

The Committee agreed that, on the basis of the evidence provided, the current scheduling of aloes for internal use, aloin, bisacodyl, colocynth (*citrullus colocynthis),* ipomoea (*ipomoea* species), jalap resin (*operculina macrocarpa),* sennosides and sodium picosulphate did not require further controls and therefore remained appropriate. The Committee recommend to New Zealand that they harmonising on the scheduling of these substances.

2. PROPOSED CHANGES/ADDITIONS TO PARTS 1 TO 3 AND PART 5 OF THE STANDARD FOR THE UNIFORM SCHEDULING OF DRUGS AND POISONS.

2.1 SUSDP, PART 1

2.1.1 INTERPRETATION OF AEROSOL CONCENTRATION

PURPOSE

The Committee considered the SUSDP interpretation of percent with regard to pressurised spray aerosols, and whether to clarify the requirements for the statement of the quantity, proportion or strength of a poison contained in a pressurised spray aerosol.

BACKGROUND

The February 2007 NDPSC Meeting considered this issue and foreshadowed:

- An amendment to Part 1 Paragraph 1.(3)(b)(ii) to clarify that reference to “per cent” in a schedule entry for a pressurised spray aerosol meant % weight in weight.
- An amendment to Part 2 Paragraph 8.(2) (by adding a new part (a)) to clarify that the most appropriate form for labelling the strength, proportion or concentration for a pressurised spray aerosol was mass of the poisons per stated mass of the preparation.

DISCUSSION

Members recalled the following from the February 2007 NDPSC Meeting:

Part 1 Paragraph 1.(3)(b)(ii)

- There appeared to be some ambiguity in interpreting what was meant by % in schedule entries when applying this to pressurised aerosol preparations.
- Paragraph 1.(3)(b) stated that "one per cent" meant "1 gram per 100 millilitres" for liquid preparations and "1 gram per 100 grams" for solid preps, but that this did not readily apply to aerosols which are liquid in a can.
- It was noted that if the proportion of poison was calculated as wt/vol, then the manufacturer could simply make the volume of the can bigger i.e. the liquefied propellant would expand to a bigger volume, resulting in a lower % wt/vol of the poison in the product, possibly descheduling it.
- A Member suggested that it would be more sensible to calculate % for these preparations as % wt/wt. The Member proposed that in paragraph 1.(3)(b)(ii) "solid or semi-solid" be replaced with "solid, semi-solid, or pressurised spray aerosol".
- Members noted that the NSW Trade Measurement Regulation 2002 required pre-packaged "aerosol products" (other than therapeutic goods) to be clearly marked with their measurement by mass (only) when packed or sold.
- Members also noted that *Therapeutic Goods Order 69* (TGO 69) “General requirements for labels for medicines” required a specific weight, or weight range, rather than %. The *Required Advisory Statements for Medicine Labels* (RASML) directly adopted SUSDP paragraph 1.(3). XXXXX confirmed that wt/actuation was used rather than % and therefore there should be no conflict between the above proposal and TGA’s requirements.

Part 2 Paragraph 8.(2)

- It was noted that Part 2, paragraph 8.(2) required that the statement of the quantity, proportion or strength of a poison, other than for human therapeutic use, must be expressed in the most appropriate of a number of forms.
- While adoption of the above proposal would mean % was to be measured as wt/wt (unless specified in the entry), the packaging requirements may allow % on the label to be expressed in an alternative form e.g. vol/vol or wt/vol if the scheduled substance is a liquid, solid or semi-solid, and the contents of the aerosol are liquid under pressure. Members therefore considered options which reflected the NSW Trade Measurement Regulation 2002’s requirement.
- The XXXXX Member also advised of a review of 20 agvet aerosol products which assessed the regulatory impact of clarifying the % labelling requirement for aerosols. This review found that all but one of the products used wt/wt.

Conclusion

- Members generally agreed that amendments to paragraphs 1.(3)(b) and 8.(2) would address both the interpretation of % for aerosols in schedule entries; and clarify that the labelling requirements should match this interpretation i.e. % means wt/wt.

Members also recalled a February 2007 NDPSC pre-meeting comment which asserted that while confirmation of an aerosol definition was useful, it was not yet clear whether or not there were specific labelling ramifications that may impact upon Trade Measurement legislation or upon international trade where wt/vol may be the regulatory standard expression.

A pre-meeting comment was received from XXXXX. Members particularly noted:

- XXXXX supported clarification of how aerosol concentrations are to be calculated and interpreted.
- With regards to companies using larger cans to avoid scheduling XXXXX advised that aerosols are generally formulated as though the contents – including propellant - were all liquid.
- XXXXX confirmed that Australia's Uniform Trade Measurement legislation requires the net contents to be stated in weight (rather than volume). This contrasts with Europe, where aerosol contents are stated in volume. Many US aerosols which fall under the purview of the FDA state their contents in volume. New Zealand legislation does not prescribe whether aerosol contents should be declared in weight or volume and dual marking (of both weight and volume) is the norm in that country.
- XXXXX had obtained (repeated) assurances from Australia's Trade Measurement Advisory Committee that dual marking of aerosols with weight and volume statements is acceptable so long as the latter is no more prominent than the (required) weight marking. XXXXX did not believe that the issue of trade measurement is germane to the issue under discussion by the Committee. For example, the European Dangerous Preparations Directive uses a wt/wt calculation for its hazard classification and yet – as noted above – labelling in Europe is in volume terms.
- If a decision may lead to changes to aerosol labelling it should be noted that aerosols, in general, do not use 'labels' but rather are constructed using lithographed tinplate or printed aluminium. This plate is printed in mass often some considerable time before being made up (by packaging companies) into aerosol cans.
- Accordingly, where aerosol labelling has had to change XXXXX have generally seen lead times of between 3 to 5 years provided to allow stooks of existing plate and cans to be exhausted, along with 'stock in trade'. XXXXX would wish such a lead time before any labelling changes were to be enforced at point of sale.
- XXXXX also sought clarification of how the proposed changes would impact on the labelling of registered pesticides as the APVMA currently require a declaration on aerosols in terms of g/kg (1.0% w/w is equivalent to 10 g/kg). [Members confirmed that wt/wt for labelling would include g/kg. It was noted that a consumer would have

to make a simple calculation to convert g/kg to % if they wished to query the scheduling status where there were % cut-offs.]

An XXXXX pre-meeting comment supported the XXXXX comment, and welcomed the intended clarification of how aerosols concentrations are to be interpreted. XXXXX wished to reinforce the above point of lead times and reiterated the XXXXX assertion that a period of 3 to 5 years was necessary.

A pre-meeting comment from XXXXX supported the February 2007 foreshadowed decision.

Members noted the argument that clarifying the interpretation of % to wt/wt need not coincide with a change to the labelling requirement for expressing %. However, this discrepancy could create a problem as it may not allow ready determination, from the % on the label, which schedule a product should be in, and could necessitate an additional calculation based on formulation, noting that formulation details may not be available. The Committee generally agreed that labelling and interpretation of % in aerosols should be consistent.

Members noted the need for a lead time with regards to a potential change to the labelling for some aerosols and agreed that a delayed implementation (from 1 January 2008 to 1 January 2009) was appropriate. It was noted that if companies had additional issues they could take these up on a case-by-case basis with the jurisdictions.

DECISION 2007/50 - 1

The Committee:

- Agreed to amend Part 1, paragraph 1.(3)(b)(ii) to clarify that reference to “per cent” in a schedule entry for a pressurised spray aerosol meant % weight in weight.
- Agreed to amend Part 2, paragraph 8.(2) to clarify that the most appropriate form for labelling the strength, proportion or concentration for a pressurised spray aerosol was mass of the poisons per stated mass of the preparation.
- Agreed to a deferred implementation date for the Part 2 amendment to 1 January 2009.

Part 1 – Interpretation – Paragraph 1 - Amendment

(3) Unless the contrary intention appears where a concentration, strength or quantity is specified in a schedule or an appendix to this Standard in respect of a substance:

(a) if the substance is present as a salt, active principle or derivative (including an ester or ether), the concentration,

strength or quantity is calculated as the equivalent amount of the substance that is listed in the Schedule or Appendix; and

(b) the expression "one per cent" means:

(i) in the case of a liquid preparation, 1 gram of the substance per 100 millilitres of the preparation; or

(ii) in the case of a solid, semi-solid or pressurised spray aerosol preparation, 1 gram of the substance per 100 grams of the preparation; and

(iii) any expression of greater or lesser percentages shall have a corresponding meaning; and

(c) in the case of codeine such concentration, strength or quantity is calculated as anhydrous codeine.

Part 2 – Labels and Containers – Paragraph 8.(2) – Amendment (Effective date 1 January 2009)

(2) if the poison is for a purpose or purposes other than human therapeutic use and:

(a) if the poison is in a pressurised spray aerosol preparation, as the mass of the poison per stated mass of the preparation;

(b) if the poison is a liquid in a liquid preparation, as the mass or volume of the poison per stated volume of the preparation;

(c) if the poison is a liquid in a solid or semi-solid preparation, as the mass or volume of the poison per stated mass of the preparation;

(d) if the poison is a solid or semi-solid in a liquid preparation, as the mass of the poison per stated volume of the preparation;

(e) if the poison is a solid or semi-solid in a solid or semi-solid preparation, as the mass of the poison per stated mass of the preparation;

(f) if the poison is a gas in a liquid preparation, as the mass of the poison per stated volume of the preparation;

(g) if the poison is a gas in a solid or semi-solid preparation, as the mass of the poison per stated mass of the preparation;

(h) if the poison is a gas in a gaseous preparation, as the mass of the poison per stated mass of the preparation;

2.1.2 REVERSE SCHEDULE LABEL FLEXIBILITY

PURPOSE

The Committee considered an amendment to the SUSDP to clarify the issue of flexibility for wording on mandated labelling arising from a reverse schedule entry.

BACKGROUND

The February 2007 NDPSC Meeting considered the labelling requirements for single use composite pack hair preparations. Following a discussion on the flexibility allowed for the wording of label statements under Appendices E and F and whether this applied to label statements mandated by reverse schedule entries, the Committee agreed to foreshadow consideration at the June 2007 NDPSC Meeting of an amendment to the "Principles of Scheduling" to explain the Committee's intent regarding flexibility for the wording of reverse schedule label statements. The proposed new paragraph was:

- Where a schedule entry for a poison requires a specific statement to be included on a label as a condition for a product to qualify for an exemption ('reverse scheduling'), then in cases where it is impracticable for a supplier to use the exact wording of such a statement, its wording may be varied provided that the full intent and meaning of the statement is not changed.

DISCUSSION

Members recalled that the pre-ambles for Appendix E and Appendix F allowed wording flexibility as set out below:

Appendix E

- "Under poisons legislation, scheduled substances and their preparations are required to be labelled with appropriate directions for first aid attention in case of poisoning. It is the responsibility of the manufacturer, packer and supplier of a drug or poison to ensure that the first aid instructions included on the label of a poison are appropriate for a specific product. The following code has been prepared as a guide for health authorities and manufacturers in drafting suitable first aid directions for this purpose. Standard statements specified in this appendix may be varied provided that the intent is not changed."

Appendix F

- "It is the responsibility of the manufacturer, packer and supplier of a drug or poison to ensure that the purchaser or user of a product is given sufficient information to be able to use it correctly and safely. Under poisons legislation, scheduled substances, which may be harmful to the user, must be labelled with appropriate warning statements and safety directions. The selection of warning statements and safety directions will depend on the formulation of the product, and the use for which it is sold and supplied. The following code has been prepared as a guide for this purpose.

  The wording of the warning statements and safety directions specified in this appendix may be varied provided the intent is not changed. Additional statements also may be added to ensure that the user of a product is sufficiently advised of its harmful nature and how to avoid deleterious effects."

Members also recalled the following from the February 2007 NDPSC Meeting:

- A Member asserted that there was need for flexibility in the specified wording for reverse scheduled labelling statements, provided the message was the same. The Member proposed adding "or words to the effect of" in reverse schedule entries.
- Several Members expressed concern over including the rider "or words to the effect", and questioned how much flexibility this would allow. The Committee generally agreed that it did not wish to be placed in the position of individually approving word variations.
- A Member noted that Appendix E and F indicated that similar words could be used provided the intent was not changed. The Member confirmed that his jurisdiction would treat reverse schedule label wording in the same way. The Member observed, however, that this would be on a case-by-case basis and that the Member would not be comfortable with "or words to the effect". The Member asserted that industry may be unduly concerned, and that a sponsor could go to a jurisdiction to get an exemption from exact wording requirements. General agreement was expressed by jurisdictional Members to being flexible with regards to the wording of such labels, and indeed that this was already current practice.
- A Member suggested that reverse scheduling label flexibility could be addressed by a statement under "Principles of Scheduling – Reading the Schedules" that indicated that the variation allowed under Appendix E or F would also apply to reverse schedule labels.

A pre-meeting comment from XXXXX also supported the foreshadowed decision. However, the majority of the XXXXX comment did not address the gazetted issued. Instead it discussed the labelling of single use composite pack hair preparations, considered at the February 2007 NDPSC Meeting. XXXXX advised that it was making arrangements for sample packaging to be provided to assist further consideration of this matter. [Members noted that XXXXX intended to consult separately with jurisdictions regarding this issue.]

A pre-meeting comment from XXXXX supported the February 2007 foreshadowed decision.

A Member noted that the reverse schedule statements had been specifically crafted and asserted that the proposed flexibility could dilute the intent. Other Members noted, however, that the proposed words "full intent and meaning" were quite specific. It was also noted that the *Required Advisory Statements for Medicine Labels* (RASML), referenced by the reverse schedule entries for human therapeutics already provided similar flexibility. Additionally, this flexibility already appeared to be practiced at the jurisdictional level.

A Member questioned whether the rider "where it is impracticable" was needed, and whether "full intent and meaning" was sufficient. The Committee generally agreed, however, that a where practicable condition would convey the message that the exact statement in a reverse schedule entry should be the norm, and variations the exception. A Member noted that if a stakeholder wished to amend the wording in the Schedule entry itself then a submission to the Committee could always be made.

A Member also noted that TGA and Medsafe did not consumer test label statements, and that allowing flexibility could perhaps allow a "better" statement to be used. Again, however, the Committee generally agreed that the exact statement in a reverse schedule entry should be the expected norm, as these statements have resulted from detailed, specific consideration by the Committee (discussion in Committee and at least 2 rounds of consultation).

DECISION 2007/50 - 2

The Committee agreed to amend the "Principles of Scheduling" to clarify the Committee's intent regarding flexibility for the wording of reverse schedule mandated label statements.

PRINCIPLES OF SCHEDULING - READING THE SCHEDULES - Amendment

Schedule entries have been designed to be as simple as possible while retaining readability, legal integrity and as much freedom from ambiguity and contradiction as possible. As a result they are expressed in a number of ways, though this number has been kept to a minimum. It is necessary to keep this variety of expression in mind when searching or interpreting Schedule entries.

Firstly, poisons are now scheduled individually using their approved names wherever practicable although exceptions are necessary in some cases. Some of those are mentioned overleaf. Older group entries are being revised and replaced by individual entries as time permits although in some of these cases a group term has also been retained to deal with any members of the group or class that may have escaped attention but should be scheduled.

Secondly, schedule entries have been expressed in either positive or negative terms and care must be taken to distinguish between the two different forms of expression. Thus, selenium is in Schedule 6 only when one of the clauses in this schedule entry applies, while fluorides are in Schedule 6 unless one of the exempting clauses applies.

Where exceptions are included in an entry these have been emphasised by printing the word “except” in bold type.

Where the schedule entries for a poison make a specific exclusion or exemption, the requirements of this Standard do not apply to that poison within the constraints of that exclusion or exemption although controls under other legislation such as pesticide registration may apply.

Where a schedule entry for a poison requires a specific statement to be included on a label as a condition for a product to qualify for an exemption ('reverse scheduling'), then in cases where it is impracticable for a supplier to use the exact wording of such a statement, its wording may be varied provided that the full intent and meaning of the statement is not changed.

Where a poison has been included in more than one Schedule the principal entry, where practicable, has been included in the most restrictive Schedule with references to the other Schedule(s) involved.

It is important to remember that a Schedule entry includes preparations containing the poison in any concentration and all salts and derivatives of the poison unless it specifically states otherwise. (See Interpretation PART 1 [paragraph 1(2)]).

It is important to note that a substance is not classed as a derivative on the basis of a single, prescriptive set of criteria. Classification of a substance as a derivative of a Scheduled poison relies on a balanced consideration of factors to decide if a substance has a similar nature (e.g. structurally, pharmacologically, toxicologically) to a Scheduled poison or is readily converted (either physically or chemically) to a Scheduled poison. However, a substance is only considered a derivative of a Scheduled poison if it is not individually listed elsewhere in the Schedules, or captured by a more restrictive group or class entry. Additionally, some entries specifically exclude derivatives. Once a substance is determined to be a derivative of a Scheduled poison, the same scheduling requirements as the Scheduled poison, including limits on access, supply and availability, will apply.

Finally, when using the Standard to determine the scheduling status of a poison it may be necessary to search each relevant Schedule as well as Appendices A, B and C and the Index. In this process if the poison is not found under its “approved name” it may be shown under a group term such as:

Group	Example
the parent acid of salts	“oxalic acid” to find sodium oxalate
the radical of a salt	“chromates” to find potassium chromate
the element	“arsenic” to find arsenic trioxide
a chemical group with similar toxicological or pharmacological activity	“hydrocarbons, liquid” to find kerosene
a pharmacological group	“anabolic steroidal agents” to find “androsterone”

AGRICULTURAL/VETERINARY, INDUSTRIAL AND DOMESTIC CHEMICALS

3. MATTERS ARISING FROM THE MINUTES OF THE PREVIOUS MEETING (CONSIDERATION OF POST-MEETING SUBMISSIONS UNDER 42ZCZ)

Nil items.

4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

4.1 LIQUID HYDROCARBONS

PURPOSE

The Committee considered the foreshadowed scheduling of hydrocarbons, liquid.

BACKGROUND

The February 2007 NDPSC meeting considered an application from XXXXX to exempt from scheduling very small volumes of liquid under the Schedule 5 entry for hydrocarbons, liquid.

XXXXX submitted an application to the APVMA to register a 99 g/L transfluthrin liquid to repel mosquitos. The product is a small 'cartridge' comprising a 1.2 mL liquid reservoir and a 'tongue' section for inserting into an electrical device. When operational, the transfluthrin liquid is heated and emanated into the air via a wick to repel mosquitoes.

The February 2007 NDPSC Meeting noted that the product is exempt under the Schedule 6 transfluthrin entry, but as it is approximately 90% hydrocarbon solvent, it would be classified as Schedule 5. XXXXX believeed that based on the exceptions under the current Schedule 5 entry, an additional exception for very small volumes of liquid is appropriate and suggested the following wording:

(i) when packed in containers each containing less than 2 mL.

The February 2007 NDPSC Meeting also noted that:

- the November 1991 DPSC Meeting agreed to exempt from scheduling liquid hydrocarbons when used as a solvent in writing correction fluids packed in containers having a capacity of 20 mL or less;

- the February 1998 NDPSC Meeting agreed to exempt from scheduling liquid hydrocarbons when used as thinners for writing correction fluids packed in containers having a capacity of 20 mL or less;

- during discussions at the above 1991 and 1998 Meetings, the Scheduling Committees noted that the volume, style of container and nature of the product made ingestion unlikely, but like all solvents, the potential for inhalation abuse existed and therefore also agreed to reconsider if a need was demonstrated in the future.

Due to an oversight in the NDPSC Secretariat, this item was omitted from the February 2007 pre-meeting gazette notice. Therefore, the Committee agreed to foreshadow a Schedule 5 amendment to exempt small volumes of hydrocarbons liquid when packed in containers each containing less than 2 mL. The Committee also agreed that a sample of the product be obtained from the applicant for viewing at the June 2007 NDPSC Meeting.

DISCUSSION

A sample of the product had been provided by the applicant and was circulated to Members.

Members agreed that the device was purpose built reducing the risk of access to a very small volume of liquid and thereby reducing the possibility of childhood poisoning.

DECISION 2007/50 - 3

The Committee agreed to confirm its foreshadowed decision to include under the Schedule 5 entry for hydrocarbons liquid to exempt volumes of 2 ml or less.

Schedule 5 - Amendment

HYDROCARBONS, LIQUID, including kerosene, diesel (distillate), mineral turpentine, white petroleum spirit, toluene, xylene and light mineral and paraffin oils (but excluding their derivatives), **except**:

(a) toluene and xylene when included in Schedule 6;

(b) benzene and liquid aromatic hydrocarbons when included in Schedule 7;

(c) food grade and pharmaceutical grade white mineral oils;

(d) in solid or semi-solid preparations;

(e) in preparations containing 25 per cent or less of designated solvents;

(f) in preparations packed in pressurised spray packs;

(g) in adhesives packed in containers each containing 50 grams or less of adhesive;

(h) in writing correction fluids and thinners for writing correction fluids packed in containers having a capacity of 20 mL or less; or

(i) in other preparations when packed in containers with a capacity of 2 mL or less.

4.2 CLOTHIANIDIN

PURPOSE

The Committee consider the scheduling of clothianidin.

BACKGROUND

Clothianidin belongs to the nitroguanidine subgroup of second generation neonicotinoid insecticides that act at the nicotinic acetylcholine receptor. Clothianidin has agonist followed by blocking activity at nicotinic acetylcholine receptors (n-ACHR), exhibiting selectivity for insect n-ACHR over mammalian n-ACHR. The second-generation neonicotinoids are characterised through being chlorothiazolyl derivatives by contrast with the first generation neonicotinoids, which are chloropyridinyl derivatives.

As a class, the neonicotinoids are seen as a broad substitute for organophosphate, carbamate and pyrethroid insecticides, exhibiting contact, stomach and systemic activity against a variety of chewing and sucking insects in both agricultural and veterinary applications.

The October 2002 NDPSC Meeting agreed that clothianidin be included in Schedule 6 on the basis of the high acute toxicity in XXXXX. The difference in the acute oral toxicity in the XXXXX did not allow establishment of a cut-off to a lower schedule.

The October 2006 NDPSC Meeting considered an XXXXX assessment of the toxicological data provided in support of the registration a product containing the active ingredient, clothianidin. XXXXX requested that XXXXX be considered for inclusion in Schedule 5. The Committee agreed to foreshadow, based on the acute toxicity, that clothianidin in preparations containing ≤ 20% clothianidin be included in Schedule 5. The Committee also requested data from an acute XXXXX study be provided.

The February 2007 NDPSC Meeting noted a comment from XXXXX indicating that it intended to have the requested XXXXX oral acute toxicity data generated and therefore requesting that further consideration of the scheduling of clothianidin be deferred until the June 2007 meeting. The Committee agreed to this deferment.

DISCUSSION

Members were advised that XXXXX provide the requested XXXXX oral acute toxicity data to XXXXX, who subsequently undertook an assessment of this information.
XXXXX

- XXXXX – the acute oral toxicity of clothianidin was low XXXXX

XXXXX

Members also recalled the following from the XXXXX report presented at the October 2006 NDPSC Meeting:

- XXXXX clothianidin had low acute oral toxicity XXXXX low dermal toxicity XXXXX and low inhalational toxicity XXXXX. It was not a skin or eye irritant XXXXX nor a skin sensitiser XXXXX. The acute oral toxicity of clothianidin was high in XXXXX Clinical signs of acute toxicity appeared to be largely related to CNS effects.

XXXXX

- As clothianidin exhibited greatest acute toxicity in XXXXX, the Committee considered it important that an acute XXXXX study on XXXXX be obtained from XXXXX.
- The report suggested that it may be appropriate to include clothianidin in preparations containing ≤ 20 % of clothianidin in Schedule 5 of the SUSDP.

DECISION 2007/50 - 4

The Committee confirmed its foreshadowed decision to include clothianidin in preparations containing ≤ 20 % of clothianidin in Schedule 5.

Schedule 5 – New entry

CLOTHIANIDIN in preparations containing 20 per cent or less of clothianidin.

Schedule 6 – Amendment

CLOTHIANIDIN **except** when included in Schedule 5.

4.3 4-AMINOPYRIDINE AND METALLIC PHOSPHIDES

PURPOSE

The Committee considered the foreshadowed amendments to the scheduling of 4-aminopyridine and metallic phosphides (including zinc phosphide).

BACKGROUND

4-Aminopyridine – prior to the February 2007 NDPSC Meeting

The November 1968 PSC Meeting considered a pest bird control product (grain impregnated with 4-aminopyridine hydrochloride) and agreed to include 4-aminopyridine in Schedule 7, noting an acute oral LD_{50} of 32.5 mg/kg for rats.

The November 1987 DPSSC Meeting noted veterinary use of 4-aminopyridines for the reversal of xylazine induced anaesthesia in cattle. The Committee concluded that Schedule 7 was inappropriate for this use and agreed to list 4-aminopyridine in Schedule 4 for therapeutic use with an Appendix D listing that "this drug should be available only for the treatment of animals" (and retained Schedule 7 for all other uses).

The February 1995 NDPSC Meeting agreed to remove 4-aminopyridine from Appendix D as there was no need to specify animal use in the Schedule 4 entry because product use pattern was a professional matter which was subject to other controls.

The May 1995 NDPSC Meeting considered a review of Appendix J, and agreed to include 4-aminopyridine in this appendix (except when included in Schedule 4).

Phosphides, metallic – prior to the February 2007 NDPSC Meeting

Metallic phosphides will produce phosphine gas in the presence of acid or water.

The November 1993 DPSSC Meeting, during a review for child-resistant closures, noted a recent death of a young boy following ingestion of a phosphide fumigation pellet similar in appearance to a throat lozenge.

Prior to August 1994, metallic phosphides were included in Schedule 6. The Appendix E entry for metallic phosphides had been amended at the November 1992 DPSSC Meeting due to concerns for the safety of hospital and ambulance personnel treating patients who had ingested metallic phosphide tablets and were exhaling phosphine gas.

The August 1994 NDPSC Meeting agreed to a proposal to include metallic phosphides in Schedule 7 and Appendix J. Inclusion in Appendix J was confirmed following a review of this appendix at the May 1995 NDPSC Meeting.

XXXXX At the October 2006 NDPSC Meeting, XXXXX provided a copy of a draft report XXXXX. The Committee noted the following from the draft report's conclusion:

- Extrapolated acute toxicity of XXXXX was commensurate with a Schedule 6 poisons schedule. The report recommended that NDPSC consider including grain based products containing ≤ 25 g/kg zinc phosphide in Schedule 6.

- The extrapolated acute toxicity of 4-aminopyridine in XXXXX was commensurate with a Schedule 6 poisons schedule. The report suggested that the NDPSC consider including grain based products containing ≤ 5 g/kg 4-aminopyridine in Schedule 6.

The Committee therefore agreed to foreshadow consideration of the scheduling of 4-aminopyridine and zinc phosphide at the February 2007 NDPSC Meeting.

The February 2007 NDPSC Meeting was advised that 4-aminopyridine and zinc phosphide were inadvertently omitted from the pre-meeting Gazette Notice. Noting that the XXXXX Members agreed to foreshadow the following decisions regarding 4-aminopyridine and zinc phosphide for consideration at the June 2007 NDPSC Meeting:

Schedule 6 – New Entries

4-AMINOPYRIDINE in preparations containing 0.05 per cent or less of 4-aminopyridine.

PHOSPHIDES, METALLIC when included in preparations containing 2.5 per cent or less of metallic phosphides.

Schedule 7 - Amendments

4-AMINOPYRIDINE **except** when included in Schedule 4 or Schedule 6.

PHOSPHIDES, METALLIC **except** when included in Schedule 6.

DISCUSSION

Members recalled the following regarding 4-aminopyridine and zinc phosphide from the XXXXX draft report XXXXX:

<u>4-Aminopyridine</u>

- Toxicology:
  - Oral LD_{50} – 20 mg/kg (rats), 4 mg/kg (dogs). In humans, poisoning with ~60 mg resulted in gastrointestinal, respiratory and neurological disturbances.
  - Repeat-dose: No information.
  - Carcinogenicity/Genotoxicity/Reproduction/Developmental: No information.
  - Other: Enhances transmission at neuromuscular junctions and other synapses. It is poorly absorbed through skin.
  - Conclusion: Acute toxicity is very high.
- 4-Aminopyridine is currently present in XXXXX products:

XXXXX

Recommendation – The extrapolated acute toxicity of XXXXX was commensurate with Schedule 6. The NDPSC may wish to consider including grain based products containing ≤ 5 g/kg 4-aminopyridine in Schedule 6.

Metallic phosphides including zinc phosphide

- Half of the substances considered by the XXXXX report were primarily used as fumigants. These substances were generally present in the gaseous phase or in a form that leads to the release of a gas. Often, the presence of the gas was difficult to detect because of a lack of colour or odour. Protection against exposure to products which consist of high concentrations of toxic gases is relatively difficult. The prescribed safety directions commonly specify the need for respiratory protection with appropriate cartridge or canister, and in a number of cases special application procedures are required. All fumigant products containing chloropicrin, 1,3-dichloropropene, ethylene oxide, methyl bromide, metallic phosphides and/or phosphine were considered to meet one or more criteria for declaration as RCPs.
- Restriction would ensure that persons authorised by the State authorities, including licensed pest control operators, have access to the chemical. Restricted access only to authorised people will prevent untrained people who are unaware of the specific requirements for use of the product from gaining access. This will protect human health. There is no detriment to the public because even under current arrangements, the public should not have access to these fumigant products.
- Toxicology:
    - Oral LD_{50} (rat) – 20-70 mg/kg (zinc phosphide) and 8.9 mg/kg (aluminium phosphide). Dermal LD_{50} (rabbit) – 2000-5000 mg/kg (zinc phosphide). The average fatal dose in human poisoning incidents was 51 g zinc phosphide. Toxic signs included shock and respiratory distress. Numbness and paraesthesia may be experienced after touching tablets.
    - Repeat-dose (rat): Reduced growth rate, signs of neurotoxicity, liver damage and anaemia after oral exposure to zinc phosphide at doses down to 5 mg/kg bw.
    - Carcinogenicity/Genotoxicity: Equivocal findings for cytogenetic effects in mice.
    - Reproduction/Developmental: No information.
    - Other: Metal phosphides are partially absorbed intact and then hydrolysed to phosphine which is released in expired air. Zinc phosphide does not release phosphine as readily as aluminium phosphide.
    - Conclusion: Acute toxicity is very high for both metal phosphides.
- There are currently XXXXX APVMA registered products containing metallic phosphides.

XXXXX

Recommendation – The extrapolated acute toxicity of the XXXXX was commensurate with Schedule 6. The NDPSC may wish to consider including grain based products containing ≤ 25 g/kg zinc phosphide in Schedule 6.

Members also recalled the following from the August 1994 NDPSC consideration of a proposal to include metallic phosphides in Schedule 7:

- The acute inhalation toxicity of phosphine was high in rats (4h LC_{50} = 15 mg/m³). The oral LD_{50} for zinc phosphide was also high (25-54 mg/kg in rats). Other metal phosphides would have similar toxicity.
- Zinc phosphide given in the diet caused increased mortality, organ weight changes and blood changes at 200-500 ppm for 13 weeks in rats (presumably this dose level was too low to cause release of phosphine at levels high enough to result in pulmonary damage or to be emitted from the animals). No effects of treatment were seen in a chronic study in which rats were fed fumigated grain containing aluminium phosphide residues at about 1 mg/kg diet for two years, or in a similar study where the average residue level was 5 ppb.
- Following ingestion of metallic phosphide tablets, lung damage is secondary to the excretion of phosphine. Other signs are severe substernal and abdominal pain, and a burning sensation. Agitation and delirium have also been reported. Pathological changes include haemorrhage of gastric mucosa, and hepatic, renal and myocardial necrosis. Less than 12 g of metallic phosphide tablets has been reported to be non-fatal, but 50 g is a fatal dose. Indian reports indicated that 1-9 g had been fatal.
- In a number of examples, from Australia and abroad, phosphine had been emitted from people who had ingested metal phosphide tablets. This posed considerable risk to health carers.
- The Committee noted that moving metallic phosphides from Schedule 6 to Schedule 7 would, in most cases, restrict their availability to licensed operators and primary producers and reduce the risk of accidental or suicidal exposure for the general public.

It was noted that while XXXXX had no particular concerns about whether the proposed Schedule 6 entries for 4-aminopyridine and metallic phosphides were general or limited to grain based preparations, the preference would be for a general entry to allow for future product development.

Several Members expressed concerns about the proposed move of low concentrations of 4-aminopyridine and the metallic phosphides to Schedule 6, noting that at least in some jurisdictions the regulation of Schedule 7 products was more robust than the corresponding regulation of RCPs. In particular:

- Several Members expressed concern about allowing 4-aminopyridine into Schedule 6 as there was potential for misuse on non-target animals. A Member noted that 4-aminopyridine was restricted by permit in his jurisdiction which did not appear consistent with a move to Schedule 6 with potential leakage to the domestic market (however, did note the precedent of a restricted substance in Schedule 6 – chloralose for pesticide use).
- The use of a linear extrapolation from animal toxicity data for 4-aminopyridine to reach a suggested oral LD_{50} for humans was queried.
- Some Members felt that the risks of phosphine poisoning were such that there should be no move to Schedule 6 for metallic phosphides (including zinc) and that the more robust Schedule 7 legislation was appropriate in this case.
- A Member noted that even if the Schedule 6 metallic phosphides entry was restricted to grain there would still be a risk of ingestion, which creates a problem not just for the person/pet ingesting but also for the persons who would be providing treatment.
- A Member advised that the use pattern of the grain based metallic phosphides product (control of rodents in a farm setting) meant that primary producers (in at least some jurisdictions) have access to such Schedule 7 products anyway, so scheduling does not really restrict legitimate access currently.
- A Member noted the very low concentration of metallic phosphides proposed for Schedule 6 capture and suggested that use in grain would limit exposure. Another Member responded that phosphine poisoning was difficult to reverse, and that phosphine gas would be liberated should the grain become wet.

A Member reiterated that should a product be designated as an RCP this would ensure that only persons authorised by the State authorities, including licensed pest control operators, have access to the chemical. A Schedule 6 entry in combination with an RCP designation would therefore not open the products for general domestic sale.

The Committee generally agreed that the Schedule 6 decision would be strongly influenced by whether these products would actually be designated RCPs (noting the draft reports current recommendation that the low concentration zinc phosphide product NOT be an RCP).

A Member advised that the APVMA's RCP consultation process was still ongoing and that the final decision on whether some or all 4-aminopyridine and metallic phosphine products would be RCP had not been made. The Committee generally felt that consideration of this issue could not progress until XXXXX final advice was in hand. Members therefore agreed to defer consideration until the October 2007 NDPSC Meeting.

A Member also noted that the rINN for 4-aminopyridine was fampridine. The Committee agreed that this should be considered as an editorial issue at the October 2007 NDPSC Meeting.

OUTCOME

The Committee agreed:

- To defer consideration of this issue until the October 2007 NDPSC Meeting to allow time for XXXXX to make a final decision on the RCP status of 4-aminopyridine and metallic phosphine products.
- To consider an editorial issue regarding the nomenclature of 4-aminopyridine at the October 2007 NDPSC Meeting, cross referencing fampridine in the SUSDP index.

4.4 PYRASULFOTOLE

PURPOSE

The Committee considered the scheduling of pyrasulfotole.

BACKGROUND

Pyrasulfotole is a benzoylpyrazole herbicide. In both plants and mammals pyrasulfotole inhibits the 4-hydroxyphenyl pyruvate dioxygenase (HPPDase) enzyme. In plants, inhibition of this key enzyme reduces carotenoid synthesis, thus leading to bleaching and weeds control. In mammals, the HPPDase enzyme is a key step in the catabolism of tyrosine. This mode of action targeting the HPPDase enzyme is shared with other herbicides such as isoxaflutole (Schedule 5) and mesotrione (does not appear to have been considered for scheduling).

XXXXX submitted data on pyrasulfotole seeking XXXXX. XXXXX supplied comprehensive toxicological studies including toxicokinetics and metabolism, acute toxicity, short-term, subchronic and chronic (carcinogenicity) studies. Genotoxicity, developmental, reproductive, neurotoxicity and (some) mechanistic studies were also supplied. A smaller range of studies were supplied on a benzoic acid derivative and these were also evaluated by XXXXX, with limited toxicity being observed.

DISCUSSION

Members noted the following key observations from the XXXXX pyrasulfotole report relevant to a scheduling consideration:

- Pyrasulfotole has low acute oral toxicity XXXXX. It has low dermal toxicity XXXXX and low inhalational toxicity XXXXX. It is not a skin irritant in XXXXX

or a skin sensitiser in XXXXX at the doses tested. However it is a moderate eye irritant in XXXXX.

- Pyrasulfotole was found to have a wide range of effects in short-term and long-term repeat dose studies, often at relatively low doses. Target organs included the eyes, thyroid, liver, kidney, gallbladder and urinary system.
- There were no reproductive effects. Developmental studies revealed no teratogenicity, although there was some foetotoxicity XXXXX in the absence of maternotoxicity in rabbits.
- Pyrasulfotole was not found to be genotoxic. Carcinogenicity studies found an incidence of eye neoplasms XXXXX and urinary tract neoplasms XXXXX at relatively high doses. These could be attributed to non-genotoxic proliferative mechanisms, and a clear threshold enabled the establishment of a NOEL in each case.
- XXXXX.
- Given that XXXXX, there was no evidence from XXXXX that would support an exemption from the requirements of scheduling for lower concentrations XXXXX

<u>Recommendation</u>

- Given the low level of acute toxicity of pyrasulfotole, the NDPSC may wish to consider placing pyrasulfotole in Schedule 5.

Members noted that no low level cut-off or other exemption was recommended, particularly as XXXXX. The recommendation reflected the expected use pattern of the product XXXXX. Whether an alternative product may present in future, i.e. for home garden use, was not considered in developing the XXXXX Schedule 5 recommendation.

XXXXX

XXXXX. With regards to the significance of the rat ocular effects for humans the XXXXX report observed that:

- XXXXX argued that effects on the cornea were related to tyrosinaemia secondary to inhibition of HPPDase by pyrasulfotole, and that they were specific to rats. XXXXX proposed that rats are especially sensitive to inhibition of this enzyme because they lack the capacity to produce p-hydroxyphenyl lactic acid (HPLA), a “diversionary metabolite” that enables reduction of plasma tyrosine concentrations when HPPDase is inhibited. XXXXX. The XXXXX evaluator noted, however, that XXXXX indicate that HPLA is indeed capable of being formed in the rat. It was also noted that dogs do not appear to be capable of producing HPLA, but despite this a chronic toxicity feeding study did not disclose any corneal lesions. This was not consistent with the hypothesis associating corneal lesions with inability to produce HPLA as a “diversionary metabolite”.

- Corneal lesions have been reported in humans treated with doses of 1-2 mg/kg bw/d of 2-(2-nitro-4-fluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC), which resembles pyrasulfotole in being an inhibitor of HPPDase. In a clinical trial of 207 patients treated with NTBC for hereditary tyrosinaemia type I, ocular side-effects were observed in some individuals, including corneal opacity in 2% of cases.
- A study reported that treatment of beagle dogs with NTBC doses as low as 0.1 mg/kg bw/d for 11 weeks produced corneal opacities. However, treatment of rhesus monkeys with 10 mg/kg bw/d for 12 weeks did not, although tyrosine values were "markedly increased". The study concluded that the production of corneal lesions in animals exposed to NTBC did not appear to be simply related to the concentration of tyrosine in ocular fluid.
- Since NTBC as a treatment for tyrosinaemia type I results in corneal opacity in a % of individuals, it was possible that pyrasulfotole exposure (which also inhibits the HPPDase enzyme) would also cause corneal effects. This may raise concerns about the exposure of the general population to such HPPDase inhibitors, which include pyrasulfotole.
- The XXXXX report noted some evidence on the relative inhibitory efficiency of mesotrione (another herbicide that inhibits HPPDase) compared with NTBC. It was noted that NTBC had a considerably longer half-life in the plasma than mesotrione and its effects on plasma tyrosine levels were more long-lasting. These results suggested that in humans mesotrione was at least an order of magnitude less effective as an inhibitor of HPPDase than NTBC. Nevertheless, corneal effects were observed in male rats treated with mesotrione at 0.48 mg/kg bw/d, with a NOEL of 0.16 mg/kg bw/d.
- No data on the comparative inhibitory effect on HPPDase of NTBC and pyrasulfotole appear to be available. However, pyrasulfotole was apparently less effective at inducing corneal lesions than mesotrione (in rat at least), XXXXX. Therefore it can be argued that pyrasulfotole was likely to be considerably less effective than mesotrione as an inhibitor of HPPDase. Since it appears that mesotrione is itself less effective than NTBC as an inhibitor of human HPPDase, it seems safe to conclude that pyrasulfotole is considerably less inhibitory of this enzyme than NTBC. This also implies that pyrasulfotole is likely not to produce corneal lesions at as low a dose level as has been observed in people treated with NTBC.
- It has been hypothesised that tyrosinaemia leads to accumulation of tyrosine in the anterior aqueous humour of the eye and tyrosine crystals are then deposited in the cornea. A similar mechanism might explain the retinal effects observed with pyrasulfotole. XXXXX

XXXXX

The XXXXX report noted that it is arguable that many of the effects of pyrasulfotole in XXXXX are the result of three separate modes of action, as follows:

- **1. Increased levels of tyrosine in the blood – tyrosinaemia – due to the effects of pyrasulfotole as an inhibitor of HPPDase.** Inhibition of this enzyme limits the normal metabolism of tyrosine and leads to a build up of tyrosine. At sufficiently high levels in the blood, tyrosine is known to cause corneal inflammation and damage. XXXXX
- **2. Pyrasulfotole precipitating out in the tissues.** XXXXX
- **3. A direct toxic effect of pyrasulfotole.** Pyrasulfotole inhibits HPPDase. Human tyrosinaemia type III involves a defect in this enzyme and has not been associated with effects on the cornea or the liver. However, when NTBC is used in human medicine as an inhibitor of HPPDase to treat tyrosinaemia type I, corneal lesions and liver effects are among those reported as adverse reactions. However liver effects are a feature of the genetic condition itself and it is not clear that these are actually side-effects. XXXXX

The Committee also noted that the XXXXX report recommended the following hazard classification statements for pyrasulfotole:

- R36 – Irritating to eyes.
- R48/22 – Danger of serious damage to health by prolonged exposure / Harmful if swallowed.
  [Members noted advice that R48/22 was applied on the basis of concerns arising from repeat-dose studies in which corneal/retinal lesions developed in animals at relatively low doses. The evaluator advised that this risk would be heavily mitigated by the ADI and PPE for the professional use product.]
- R63 – Possible risk of harm to the unborn child.
  [Members noted that R63 was applied because of the occurrence of foetotoxicity in the absence of maternotoxicity in a rabbit developmental study.]

Members also noted the following cut-off concentrations were recommended to apply to the above hazard classification statements:

- $\geq 20\%$ R36, R48/22, R63
- $10\% \leq \text{Conc} < 20\%$ R48/22, R63
- $5\% \leq \text{Conc} < 10\%$ R63

XXXXX

The XXXXX report also noted that the effects of pyrasulfotole may be compared to those observed in studies previously assessed XXXXX on isoxaflutole, which resembles

pyrasulfotole chemically, as well as in its mode of action as an inhibitor of HPPDase. Isoxaflutole also produced corneal opacity, XXXXX. Isoxaflutole was placed in Schedule 5 at the May 1997 NDPSC Meeting, and the Committee at that time considered the corneal lesions effect to be species specific (rat) and not relevant to isoxaflutole in man at very small exposure levels.

A Member noted the carcinogenic findings, but asserted that this was of little concern as this was only observed at high concentrations with good evidence that pyrasulfotole was not genotoxic. The acute toxicity data was consistent with Schedule 5.

A Member also noted that the evidence on the ocular effects of pyrasulfotole seemed inconsistent. There was a suggestion that there was a species specific susceptibility for these effects in rat, yet the dog studies did no necessarily support this theory. However, there was a clear no effect level observed.

Given the questions about the ocular effects, a Member felt that the Committee's consideration would have been assisted had human exposure data been supplied, particularly given the observation of corneal lesions in humans following exposure to a substance which also inhibited HPPDase (NTBC). The Member specifically mentioned the benefit of data on exposure of possibly sensitive individuals such as those with tyrosinaemia. The Member did agree that the data suggested pyrasulfotole was much less active than NTBC in relation to this effect.

A Member, noting that tyrosine is a precursor to thyroid hormone and that the XXXXX studies had mentioned thyroid changes, queried whether there was concern regarding thyroid effects in humans. The Committee noted, however, that the data supported the conclusion that the thyroid effect was species specific XXXXX and was not an issue for other species, including human.

Another Member agreed that while pyrasulfotole had low toxicity, it also had a variety of effects that could be produced in laboratory animals at relatively low doses which were of some concern. Indeed, there appear to be a number of pathological aspects of these exposures that had yet to be explained. Members generally agreed with the evaluator, however, in that exposure was likely to be well below the level that might give rise to the various effects, particularly the ocular effects and retinal changes.

Several Members noted that the application was for commercial/agricultural use and did not address potential domestic use allowed by a Schedule 5 entry. The Committee strongly agreed that pyrasulfotole should not be allowed on the domestic market because of questions regarding some of the observed effects. A Member suggested, and the Committee endorsed, that XXXXX recommend to APVMA that no pyrasulfotole product for domestic use should be registered, and that any product labelling for pyrasulfotole include 'not for home garden use' or similar.

DECISION 2007/50 - 5

The Committee agreed to include a new entry for pyrasulfotole in Schedule 5 as:

- Pyrasulfotole is a moderate eye irritant.
- Pyrasulfotole has low acute toxicity by the oral, dermal and inhalation routes, and is not a skin irritant or sensitiser.

Schedule 5 – New entry

PYRASULFOTOLE.

4.5 2,4-DICHLOROPHENOXYACETIC ACID (2,4-D)

PURPOSE

The Committee considered the scheduling of 2,4-dichlorophenoxyacetic acid (2,4-D) deferred from the February 2007 NDPSC Meeting.

BACKGROUND

The October 2006 NDPSC Meeting considered a draft review of 2,4-D under the APVMA's Chemicals Review Program. Members noted that the review outcomes had not been concluded by APVMA; however it was understood that the focus of their remaining work was on environmental concerns. It was suggested that if changes to 2,4-D scheduling was foreshadowed as suggested by XXXXX, then the final outcome of the review could also reflect the scheduling outcomes including expected industry comment. The Committee agreed to foreshadow that, based on its acute toxicity, 2,4-D be included in Schedule 6 with a cut-off to Schedule 5 for preparations containing ≤ 20 % 2,4-D.

The February 2007 NDPSC Meeting noted advice that the review of 2,4-D may not be concluded until the end of 2007. Members agreed that it would be desirable to conclude all considerations on 2,4-D at the same time. The Committee also noted that public health concerns had been identified and that it was desirable that these be addressed as soon as possible. The Committee therefore agreed that the scheduling decision on 2,4-D be deferred until the June 2007 NDPSC Meeting when the extent of progress by the APVMA on the wider review of 2,4-D would be known.

DISCUSSION

Members noted the following advice regarding the APVMA review of 2,4-D:

XXXXX

The Committee noted XXXXX preference for consideration to be deferred until completion of the APVMA review process, in particular the desire to afford natural justice through a right of reply by stakeholders to the XXXXX report. However, some Members reiterated the need to move forward with a consideration of the scheduling of 2,4-D, noting the February 2007 conclusion that public health concerns had been identified and that it was desirable that these be addressed as soon as possible.

Members recalled the following from the XXXXX report on 2,4-D:

Acute Toxicity

XXXXX

- The acute oral toxicity of 2,4-D appears to have been hitherto underestimated. The XXXXX suggested that the new data supported the inclusion of 2,4-D (including all salts and esters) in Schedule 6. XXXXX
- XXXXX, the XXXXX suggested that a possible cut-off to Schedule 5 could be set at 20 % irrespective of its form (i.e. 2,4-D, its salts and esters).

A Member, noting that the Committee had the toxicology data before it, enquired as to the disadvantages of making a scheduling decision at this time. A Member advised that the main draw back to making a decision at this Meeting was that this could pre-empt the APVMA process and would perhaps be seen as denying natural justice to those stakeholders who provided data for the review but who have not seen the XXXXX report and have yet to be given the opportunity to respond.

A Member noted that products containing 2,4-D would all be registered through the APVMA, and that there were no unregulated domestic products which needed to be urgently captured by scheduling. The Member asserted therefore that all 2,4-D products were going through a public health and safety assessment with the appropriate regulatory authority (the APVMA).

Other Members, however, noted that the Committee had the toxicological data, and the XXXXX report's recommendation, which supported a rescheduling from Schedule 5 to Schedule 6, yet products were currently available on the market as Schedule 5, and would remain so until this issue was addressed by the Committee. Also, epidemiological data that is available might suggest that human toxicity is of concern and hence the need to consider rescheduling quickly.

The Committee generally agreed that an open ended deferment of scheduling consideration for 2,4-D to await completion of the APVMA review was not appropriate. However, it was agreed that an additional short period could be accommodated which would hopefully see finalisation of the APVMA review, particularly if this were to allow

time for stakeholders to respond to the XXXXX report when this was released by APVMA.

Members agreed that an acceptable balance between the benefit from allowing APVMA a reasonable time period to complete its process, and the risk inherent with having 2,4-D products in the market as Schedule 5 products, would be to foreshadow consideration of the scheduling of 2,4-D at the February 2008 NDPSC Meeting.

OUTCOME

The Committee agreed to foreshadow consideration of the scheduling of 2,4-D at the February 2008 NDPSC Meeting.

FORESHADOWED DECISION (for consideration at the February 2008 Meeting)

Schedule 5 – Amendment

2,4-D in preparations containing 20 per cent or less of 2,4-D.

Schedule 6 – New Entry

2,4-D **except** when in Schedule 5.

6. MATTERS REFERRED BY THE AUSTRALIAN PESTICIDES AND VETERINARY MEDICINES AUTHORITY.

6.1 DIQUAT

This item was withdrawn by XXXXX prior to the Meeting.

6.2 TRILOSTANE

PURPOSE

The Committee considered the scheduling of trilostane.

BACKGROUND

XXXXX submitted a toxicology data package seeking the approval of a new veterinary therapeutic substance, trilostane. XXXXX

Trilostane is a 4α 5-epoxy steroid and is an effective inhibitor of adrenal steroidogenesis in laboratory animals and humans. Trilostane antagonises the activity of exogenous adrenocorticotrophic hormone (ACTH) and inhibits the 3β hydroxysteroid

dehydrogenase-isomerase enzyme system, blocking the production of the glucocorticoids (cortisol and corticosterone) and aldosterone. The principle metabolic effect of this inhibition is an increase in pregnenolone and 17-OH pregnenolone, both of which are biologically inactive. Other secondary pharmacological effects include the inhibition of aldosterone synthesis stimulated by sodium deficiency, anti-hypertensive effects, and decreased production of glucocorticoids, liver tryptophan pyrrolase and prevention of ACTH induced increase in urinary 17-ketosteroids.

In the UK trilostane is used as a human medicine for use in adreno-cortical hyperfunction and post-menopausal breast cancer. In 2005, trilostane products were also approved for veterinary use in the UK. There are no current therapeutic equivalents containing trilostane in the US. Trilostane is not listed on the ARTG.

Trilostane has also been used (prior to prostaglandin administration) in labour induction abortion in the second trimester, particularly in developing countries because antiprogestins are either not available or unaffordable.

DISCUSSION

The XXXXX evaluation report drew the following conclusion regarding scheduling:

- Except for the potential for high skin and eye irritation, the acute toxicity profile of trilostane is low. It is not carcinogenic and is unlikely to be mutagenic in vivo.
- Based on its intended use as a therapeutic agent requiring professional veterinary diagnosis and management, the NDPSC may consider that Schedule 4 is appropriate for trilostane.

Members also noted the following points from the XXXXX evaluation report:

- Most of the studies submitted had been conducted in the 1960's and 1970's and were not consistent with contemporary GLP standards. Although the studies submitted were relatively old, they provided data for a satisfactory assessment and derivation of conclusions.
- Trilostane has low acute oral toxicity XXXXX. It is expected to be of low acute dermal and inhalational toxicity. Data on skin and eye irritation or skin sensitisation characteristics were not available.

XXXXX

- Trilostane has been used in human medicine for over 20 years for the treatment of breast cancer. There are several reports of successful treatments of Cushing's syndrome, although more recently there have been reports bringing into question the effectiveness of this treatment following publication of mixed results giving wide individual variation. Generally, side effects in humans are rare at the recommended dose of 120–480 mg/day, but nausea, vomiting, diarrhoea and oedema of the palate

have been reported at higher doses (i.e. 500–1000 mg/day). Side effects have also been seen if the initial dose is increased too quickly, and hyperkalaemia may occur if trilostane is given concurrently with potassium sparing diuretics. Overuse can precipitate an Addisonian crisis although cessation of treatment usually results in a rapid and complete recovery. Trilostane is contraindicated in pregnancy and for those trying to conceive. It may interfere with oral contraceptives, and has been reported to cause a significant fall in serum testosterone levels. The data show that the side effects of trilostane are usually mild and rapidly resolve upon cessation of treatment.

- A published paper on a clinical trial involving human volunteers showed that trilostane caused a significant decrease in progesterone and oestradiol production, resulting in a concomitant reduction in induction-to-abortion interval. Based on these findings it has been concluded that trilostane is an effective pre-treatment agent in mid-trimester termination of pregnancy.
- The findings in developmental toxicity studies demonstrate that continued administration of trilostane during pregnancy affects the maintenance of pregnancy resulting in increased foetal resorption. XXXXX

XXXXX

Members were advised that trilostane was already in limited veterinary use in Australia. A Member noted that trilostane would offer a useful adjunct to the treatment of canine Cushing's syndrome, but this would certainly require veterinary diagnosis and management. The Committee agreed that a Schedule 4 entry would be appropriate.

The Committee noted that trilostane had been used for human therapeutic use overseas. It was generally agreed that the Schedule 4 entry should therefore capture all patterns of use, not just animal therapeutic use. While there was currently no Australian registered human therapeutic product it was noted that there were avenues for importing unregistered human therapeutics which warranted control by a Schedule 4 listing. Additionally, Members were advised that trilostane had been brought into Australia on several occasions through the Special Access Scheme.

A Member noted that some of the evaluated studies were old and that reliance on these was yet another reason why Schedule 4 was appropriate.

DECISION 2007/50 - 6

The Committee agreed to include trilostane in Schedule 4 as it was highly irritant to the skin and eye, and the conditions being treated (either human or animal) required professional diagnosis and management.

Schedule 4 – New entry

TRILOSTANE.

6.3 PYRIPROLE

PURPOSE

The Committee considered the scheduling of pyriprole.

BACKGROUND

XXXXX had sought approval of a new active constituent pyriprole, XXXXX

Pyriprole belongs to a class of insecticides known as phenylpyrazoles. The toxicity of phenylpyrazoles to insects and mammals is attributable to their action at the gama-aminobutyric acid (GABA) regulated chloride channel, disrupting CNS activity.

DISCUSSION

Members were advised that XXXXX had aired strong concerns about the time frames for scheduling of pyriprole. Members were advised:

- The June 2006 NDPSC consideration of sulfentrazone caused concern because the evaluation report was submitted to the Committee for scheduling consideration prior to the report being provided to the sponsor (i.e. the sponsor was unable to exercise a right of reply to the reports conclusions prior to scheduling).
- In light of the above it had been agreed that the following processes would take place when a veterinary (or agricultural) substance was brought to the Committee for consideration of scheduling:
    - An application is made to the APVMA.
    - APVMA provides the relevant parts of the application to XXXXX for a health risk assessment (noting that the assessments that XXXXX carry out for the APVMA take place with separate time lines to the meeting cycle of the NDPSC).
    - An XXXXX report is provided to APVMA who in turn provide a copy to the applicant to allow a right of reply regarding the XXXXX risk assessment report.
    - Should the XXXXX report include scheduling recommendations, the Secretariat would include the substance in a pre-meeting gazette.
- The XXXXX pyriprole report was due to the APVMA on 4 June 2007. As this date was well past the publication date of the pre-meeting gazette (24 April 2007), pyriprole was not included in that gazette notice.
- XXXXX had noted the date the XXXXX report was due and from that assumed that the pyriprole scheduling consideration would occur at the June 2007 NDPSC Meeting. XXXXX claimed that commercial disadvantage would arise if pyriprole was not considered at the June 2007 NDPSC Meeting.

- In light of XXXXX concerns, it was agreed, in consultation between the Chair and Secretariat, to take the extraordinary step of gazetting a separate notice for pyriprole for the June 2007 Meeting.
- An applicant is usually allowed time to comment on an XXXXX report before it is considered by the Committee. However, as pyriprole was gazetted at such a late date, there was no time for the applicant to provide comment before pyriprole was to be considered. XXXXX was made aware of this fact.
- The XXXXX subsequently advised APVMA that it was unable to complete the risk assessment elements of the submission without additional information. [Members noted XXXXX advice that those parts of the evaluation report awaiting information to be completed were mostly to do with exposure, and that the completed portions of the XXXXX report may be sufficient to allow a scheduling decision to be made].

Members noted the XXXXX evaluation report's conclusion that, based on the toxicological profile of pyriprole (moderate dermal toxicity, XXXXX the NDPSC may consider pyriprole appropriate for inclusion in Schedule 6.

Members also noted the following from the evaluation report:

XXXXX

- Of 23 toxicological studies submitted for pyriprole, 22 studies were relied on. XXXXX. All relied on studies were conducted in accordance with GLP and contemporary test guidelines, and were considered adequate for the assessment of the toxicology profile of pyriprole.
- Pyriprole had low acute oral and dermal toxicity in XXXXX, and moderate acute dermal toxicity in XXXXX. Pharmacokinetic studies indicated that pyriprole was absorbed through the skin, but due to its fast metabolism and clearance, it was not detected in plasma. Pyriprole is distributed in fur within one day after topical treatment. The concentration in the hair decreased with time but was detectable for at least 30 days after treatment. [Members noted that XXXXX had written to XXXXX seeking additional data on the persistency of pyriprole – see below].
- Pyriprole is not a skin or eye irritant in XXXXX and is not a skin sensitiser.
- XXXXX
- Pyriprole had no effect on reproductive parameters in XXXXX and showed no teratogenic effects in XXXXX. Pyriprole is not mutagenic. No long term toxicology studies or carcinogenicity studies were provided. However, based on XXXXX pyriprole is unlikely to pose a carcinogenic risk to humans.

XXXXX

- With the available toxicology information, XXXXX had classified pyriprole as a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances* with the following risk phrases:

  R21 (Conc. ≥ 25%) Harmful in contact with skin

XXXXX

Members also noted that XXXXX wrote to XXXXX advising that it was unable to complete the risk assessment elements of the submission without additional information from XXXXX in response to the following:

- XXXXX Does XXXXX have any information or comments on the rates at which pyriprole may be transferred to humans through petting and grooming of XXXXX, particularly by children?
- Given the persistence of pyriprole in skin and hair, does XXXXX have any information or comments on the potential for pyriprole to bioaccumulate in humans following monthly treatment and handling of XXXXX?
- XXXXX had noted that the toxicokinetic studies were performed on XXXXX but the toxicology studies were mainly performed on XXXXX. Does XXXXX have any information or comments on the comparative metabolism of pyriprole in XXXXX and XXXXX?
- XXXXX
- Does XXXXX have any other comments related to the persistence and bioaccumulation of the active and the product?

XXXXX wrote to XXXXX in response to the XXXXX assessment report. This letter was cc'd to the Secretariat after the cut-off date for public comment for the special gazette notice for pyriprole. [Members noted that XXXXX was made aware that its submission had not been received in time and would only be considered at the discretion of the Committee. The Committee subsequently agreed to consider this comment, but also agreed that this did not set a precedent for consideration of late comments]. This letter raised concerns about the XXXXX reports recommendations and stated that Schedule 6 was not the appropriate schedule for pyriprole.

To support this argument, the scheduling of fipronil was drawn on and a comparison made between the toxicology of the two substances. Currently the Schedule 5 cut-off for fipronil is ≤ 10% (with an exemption from scheduling for ≤ 0.05%). XXXXX stated that, given this information, pyriprole should be included in Schedule 5 with a cut-off of 12.5% or less.

XXXXX

Members noted that XXXXX had written to XXXXX regarding, and countering, the above argument. XXXXX did not support the requested Schedule 5 cut-off (≤ 12.5%) for pyriprole as the oral LD_{50} in XXXXX was between XXXXX, consistent with Schedule 6, and XXXXX is a slight eye irritant. XXXXX also noted that the fipronil concentrations and cut-offs were based on evaluation of an extensive toxicity data package, not on a class entry or any comparison with surrogate data. Therefore, XXXXX confirmed its original assessment's finding that the toxicity profile of XXXXX did not warrant a Schedule 5 cut-off.

A Member noted that the abnormally high dermal susceptibility of XXXXX was interesting, given that the pattern of use (externally on pets) had a clear potential for transfer to humans, including children. The Member felt that it would have been reassuring if the likely hazard for humans in this situation had been more fully addressed.

The Committee generally agreed that while there was sufficient data indicating the appropriateness of a Schedule 6 parent entry for pyriprole, the data underpinning the Schedule 5 cut-off proposal was limited. Indeed, it was concluded that the toxicity of low concentrations of pyriprole remained largely unknown (unlike the fipronil case where extensive toxicity data was available). Members also noted that the limited data that was supplied appeared to actually support Schedule 6 – the data indicated that XXXXX had oral LD_{50} XXXXX between XXXXX. This was higher than the active alone so it was possible that it was a formulation issue, but there was insufficient data to discount toxicity concerns, particularly in conjunction with the acute toxicity of pyriprole XXXXX and lack of knowledge regarding human susceptibility. This inconsistency was explained with information that was brought to light subsequent to the Meeting – see below.

DECISION 2007/50 - 7

The Committee agreed to include a new entry in Schedule 6 for pyriprole as the toxicological risks can be appropriately reduced through packaging and labelling.

Subsequent to the Meeting it was brought to the Committee's attention that an error had been detected in the evaluation report. In the report tabled considered at the Meeting the acute oral LD_{50} in XXXXX was stated to be XXXXX. XXXXX advised that the correct value was XXXXX. The Members reconsidered, and confirmed, the above decision in light of this correction.

Schedule 6 – New entry

PYRIPROLE.

7. MATTERS REFERRED BY OFFICE OF CHEMICAL SAFETY (OCS) BRANCH

7.1 FORMALDEHYDE AND PARAFORMALDEHYDE

PURPOSE

The Committee considered the scheduling of formaldehyde and paraformaldehyde, including recommendations from the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) formaldehyde Priority Existing Chemical (PEC) Assessment Report.

BACKGROUND

Formaldehyde is a colourless gas with a pungent, irritating odour produced commercially by the catalytic oxidation of methanol. Formaldehyde (and paraformaldehyde) is mainly used in the manufacture of formaldehyde-based resins, which are widely used in a variety of industries, predominately the wood industry. Formaldehyde is also used in medicine-related industries (such as forensic/hospital mortuaries and pathology laboratories), embalming in funeral homes, film processing, textile treatments, leather tanning, and a wide range of personal care and consumer products. The concentrations of formaldehyde in these products range from 40% (in embalming and film processing solutions) to < 0.2% (in the majority of cosmetics and consumer products).

The August 1991 DPSSC Meeting considered a review of the toxicology of formaldehyde. The Committee noted that although some epidemiology suggested an association between increased exposure to formaldehyde and increased incidence of some tumours, this was not supported by other studies. In addition, animal studies consistently failed to produce tumours other than at the site of initial contact (nasal cavity and stomach), a not uncommon finding with irritant materials. Such tumours were seen only in the rat. The Committee therefore agreed that Schedule 6 remained appropriate for formaldehyde with an exception for ≤ 5%.

The November 1999 NDPSC Meeting noted that formaldehyde and paraformaldehyde, for most practical purposes, are the same compound. Paraformaldehyde consists of short chain polymers of 8-100 units of formaldehyde and readily dissociates to form gaseous formaldehyde when heated or dissolved in water. Members therefore agreed to create entries for paraformaldehyde mirroring the formaldehyde entries.

The February 2000 NDPSC Meeting considered a harmonisation proposal to include formaldehyde and paraformaldehyde in Schedule 2 for human therapeutic use with an exception for ≤ 5% formaldehyde/paraformaldehyde. The May 2000 NDPSC Meeting agreed to the proposal with a variation to the exception – instead of ≤ 5% formaldehyde/paraformaldehyde, it became ≤ 5% formaldehyde for both the formaldehyde and paraformaldehyde entries.

DISCUSSION

Members noted the following from the formaldehyde PEC Assessment Report (http://www.nicnas.gov.au/Publications/CAR/PEC/PEC28/PEC_28_Full_Report_PDF.pdf), and also noted the substantial public consultation process in relation to this report:

- Formaldehyde was declared a PEC in March 2002 in response to occupational and public health concerns, including its sensitisation potential and carcinogenicity.

Recommendations

- The assessment included a number of recommendations. Recommendation 15 was that the Committee consider amending the current scheduling for formaldehyde and paraformaldehyde taking note of the following:

  1) the need to consider more restrictive categories given its potency of causing skin sensitisation and its classification for the workplace as a Category 2 carcinogen;

  2) the need for more protective cut-off values for cosmetics and personal care products containing formaldehyde. The EU cut-off values were highlighted as representing a potential best practice model and have the following restrictions:

  - Formaldehyde and paraformaldehyde (as a preservative) for cosmetic use:
    - free formaldehyde at 0.2% or less in all cosmetic preparations [except oral hygiene preparations, nail hardeners and aerosol dispensers (sprays)];
    - free formaldehyde at 0.1% or less in oral hygiene preparations;
    - free formaldehyde at 5% or less in nail hardeners; and
    - use of formaldehyde and paraformaldehyde in aerosol dispensers (sprays) is prohibited.
- Members also received a separate NICNAS recommendation regarding non-cosmetic domestic products, discussed below.

Health effects

- The critical health effects of formaldehyde for risk characterisation were sensory irritation, skin sensitisation and carcinogenicity.
- In humans and experimental animals, formaldehyde was readily absorbed by all exposure routes. When inhaled, it reacted rapidly at the site of contact and was quickly metabolised in the respiratory tissue.
- Following acute exposure via inhalation, dermal and oral routes, formaldehyde was moderately toxic in animals. Humans experience sensory irritation (eye, nose and respiratory tract irritation) at levels in air $\geq$ 0.5 ppm.
- Evidence clearly indicates that formaldehyde solution is a skin irritant and a strong skin sensitiser.

- The available human and animal data indicate gaseous formaldehyde was unlikely to induce respiratory sensitisation. Limited evidence indicates that formaldehyde may elicit a respiratory response in some very sensitive individuals with bronchial hyperactivity, probably through irritation of the airways.
- No systemic toxicity was observed following repeated exposure to formaldehyde in animals and humans. Effects at the site of contact show clear dose-related histological changes (cytotoxicity and hyperplasia). An inhalation NOAEL of 1 ppm (1.2 mg/m^3) and an oral NOAEL of 15 mg/kg bw/day were identified for histopathological changes to the nasal tract and the fore- and glandular stomach in the rat, respectively.
- Formaldehyde was clearly genotoxic in vitro, and may be genotoxic at the site of contact in vivo. Overall, formaldehyde was considered to have weak genotoxic potential.
- The possible relationship between formaldehyde exposure and cancer has been studied extensively in experimental animals and humans. There was clear evidence of nasal squamous cell carcinomas from inhalation studies in the rat, but not in the mouse and hamster. Although several epidemiological studies of occupational exposure to formaldehyde have indicated an increased risk of nasopharyngeal cancers, the data are not consistent. The postulated mode of action for nasal tumours in rats was biologically plausible and considered likely to be relevant to humans.
- There were also concerns of an increased risk for formaldehyde-induced myeloid leukaemia, however, the data was not considered sufficient to establish a causal association. There was no postulated mode of action to support such an effect.
- Based on the available nasopharyngeal cancer data, formaldehyde should be regarded as if it may be carcinogenic to humans following inhalation exposure. Formaldehyde meets the NOHSC Criteria for a Category 2 carcinogen (R49, may cause cancer by inhalation). Other classifications that remain applicable are: toxic by inhalation, in contact with skin and if swallowed (R23/24/25), causes burns (R34), and may cause sensitisation by skin contact (R43).
- Based on animal and limited epidemiology data, formaldehyde was unlikely to cause reproductive and developmental effects at exposures relevant to humans.
- The best available LOEL for non-cancer effects in humans is 0.5 ppm for sensory irritation.
- A 2-stage clonal growth model was developed to assess the respiratory carcinogenic risk of formaldehyde to humans. The model was considered a more reliable estimate of cancer risk than the use of standard default assumptions, due to the incorporation of all available biological data. Key estimates of the human carcinogenic risk for public and occupational exposure (for non-smokers) using this model were:
-

Exposure Concentration	Predicted Additional Respiratory Cancer Risk	
	Public	Occupational
0.10 ppm (100 ppb)	≈ 0.3 in 1 million	≈ 0.05 in 1 million
0.30 ppm (300 ppb)	≈ 1 in 1 million	≈ 0.2 in 1 million
1.00 ppm (1000 ppb)	≈ 33 in 1 million	≈ 50 in 1 million

Public exposure and health risks

- The estimated environmental exposures to formaldehyde indicate maximum annual average concentration in urban air is 5.5 ppb and maximum 24-h average is 23.5 ppb. The public health risk of respiratory tract cancer after repeated exposure to formaldehyde levels in ambient air is low. The risk of sensory irritation to the public is also low at the estimated formaldehyde levels in ambient air.
- Due to public concern of childhood chemical exposure and cancers, together with the findings of relatively high levels of formaldehyde in mobile homes and relocatable buildings, a worst-case scenario risk estimation incorporating higher exposures during childhood was conducted. The worst-case scenario was children who live in mobile homes and spend all their schooling time in relocatable classrooms up to 17 years of age. The predicted additional risk of respiratory tract cancer for a full 80-year lifetime, including childhood exposure to formaldehyde under the worst-case scenario, was low at 0.45 in a million.
- The general population may also come into skin contact with formaldehyde solutions due to its use in a wide range of cosmetics and consumer products. However, the majority of the products contain formaldehyde at low concentrations (< 0.2%). Because formaldehyde solutions may induce skin sensitisation and even very low concentrations of formaldehyde in solution may elicit a dermatological reaction in individuals who have been sensitised, dermal exposure should be minimised or prevented wherever possible.
- The direct and indirect exposure of the general public via cosmetic and consumer products is expected to be widespread and repeated. Overseas countries, such as the EU, have restrictions on use of formaldehyde in cosmetic products;
- The assessment report also recommended that government organisations such as APVMA and TGA take the findings of the human health hazard assessment into consideration in future work on formaldehyde or products containing formaldehyde, noting use of formaldehyde in therapeutic and agricultural and veterinary products.

Cosmetics and consumer products

- Formaldehyde functions as a drying agent, surfactant or preservative in cosmetics and consumer products, such as homecare products and household cleaning products. The following NICNAS table lists reported products containing formaldehyde.

Cosmetics and personal care products	Shampoos and conditioners Shower gels Liquid hand soaps Cream cleansers Skin moisturiser Toothpastes Nail hardeners
Household cleaning products	Sink detergent Toilet cleaner Stainless steel cleaner Glass cleaner Leather cleaner Laundry liquid cleaners/sprays Surface liquid cleaners Floor cleaner Rinse aid Carpet cleaners Dishwashing liquids
Homecare products	Fabric conditioners/softeners Fabric wash Wool wash

- Skin contact is the principal route of direct exposure, but exposure can also occur via eyes, mucous membranes, and respiratory epithelium. Small amounts of aqueous formaldehyde were also likely to be ingested during use of oral hygiene products. Therefore, although at low concentrations, direct exposure to formaldehyde was expected to be widespread and repeated with total exposure varying greatly, depending on the formulation and product type, route of exposure, individual habits and practices.
- Because of its high reactivity with biological macromolecules and rapid metabolism, formaldehyde exposure via the skin and inhalation is unlikely to cause systemic toxicity. The main concern as a consequence of cosmetic and consumer exposure remains at site of contact. Although concentrations of formaldehyde in these products are generally low, the direct exposure via cosmetic and consumer products is expected to be widespread and repeated.
- The majority of cosmetic products used in Australia contain < 0.2% free formaldehyde. However, some products, such as nail hardener, contain up to 1% formaldehyde. Other reported products containing > 0.2% formaldehyde include concentrated fabric softener (0.3%), concentrated detergent (0.3%) and concentrated dishwashing liquids (0.6%).

- Overseas publications report the formaldehyde content of some cosmetics as high as 4.5% (in nail hardeners) and concentrations in dry skin lotions, crème rinses and bubble bath oil are in the range of 0.4% to 0.6%.
- There was no Australian standard limiting the amount of formaldehyde allowed in cosmetic products. The Australian cosmetics industry follows international practice based on the Cosmetic Ingredient Review (CIR) reports for formaldehyde (CIR Expert Panel, 1984) and formaldehyde donor products, such as DMDM Hydantoin (CIR Expert Panel, 1988). These reports concluded that the concentration of free formaldehyde should not exceed 0.2% and aerosolised cosmetic products containing formaldehyde should not be used. These reports have been reviewed recently and no changes have been made (CIR, 2003; CTFA, 2003).
- In the EU, Annex VI (List of preservatives which cosmetic products may contain) of the Cosmetics Directive 76/768/EC (EC, 1999) requires that all finished products containing formaldehyde or substances listed in the Annex which release formaldehyde must be labelled with the warning 'Contains formaldehyde' where the concentration of formaldehyde in the finished product exceeds 0.05%. The maximum authorised concentration of free formaldehyde and paraformaldehyde is 0.2% in cosmetic products, except for oral hygiene products where the maximum concentration of free formaldehyde is 0.1%. Use of formaldehyde and paraformaldehyde in aerosol dispensers (sprays) are prohibited. Formaldehyde is also listed in Annex III of Cosmetics Directive 76/768/EC (a list of preservatives which cosmetic products must not contain except subject to the restrictions and conditions laid down due to toxicological concerns), which limits the maximum authorised concentration in nail hardeners to 5%. The Annex also states that nail hardeners with > 0.05% formaldehyde as a preservative must carry the warning statement of 'Protect cuticles with grease or oil. Contains formaldehyde'.
- In Canada, formaldehyde is acceptable for use in non-aerosol cosmetics provided that it does not exceed 0.2%. In addition, the recommended limit for formaldehyde concentration in cosmetics is less than 0.3% except for nail hardeners, for which a maximum concentration of 5% is recommended.

Members were also advised that NICNAS wished to comment on the scheduling of non-cosmetic domestic products which was not addressed in the PEC reports recommendations. XXXXX:

- Advised that a more conservative cut-off than the current 5% (formaldehyde or paraformaldehyde) should be applied to non-cosmetic domestic products.
- Noted that there was no information in the formaldehyde PEC report on overseas restrictions applying to non-cosmetic domestic products.
- Recommended that the cut-off be reduced from 5% to 0.2% as:
    - Formaldehyde is a potent skin sensitiser.

- No threshold had been identified for this sensitisation. Members noted that the PEC report indicated that the best available LOEL for non-cancer effects in humans was 0.5 ppm for sensory irritation.
- There should be consistency between the cut-off for cosmetics and that for other domestic products. A Member noted, however, that the exposure pattern for the risk of skin sensitisation may differ between cosmetics and other domestic products.
- The current level of formaldehyde or paraformaldehyde in most such products was already ≤ 0.2%. A Member noted, however, that the PEC report indicated a number of products contained > 0.2% formaldehyde such as concentrated fabric softener (0.3%), concentrated detergent (0.3%) and concentrated dishwashing liquids (0.6%).

Members noted the following from XXXXX pre-meeting comment:

- For industry the NICNAS PEC had changed the Classification and Risk Phrase for products with > 0.1% formaldehyde. This had lowered the threshold for industrial products with trace formaldehyde from 0.2% to 0.1% to become Hazardous substances.
- Many companies don't know they have this trace level present and many have worked hard to keep their level < 0.2% so their product would not be classified as Hazardous - Sensitiser. It would be very hard to be below 0.1% free formaldehyde.
- Queried whether such trace levels of formaldehyde (0.1-0.2%) really present a cancer inhalation hazard, noting that the PEC report seems to decide this is so.
- Queried, for domestic products, such a cancer inhalation risk at the 0.1-0.2% levels, asserting that there was probably not a risk at <1% free formaldehyde. Asserted therefore that there was no need to advise of cancer inhalation risk at <1% free formaldehyde in domestic products. Members noted that no evidence was supplied in support of these assertions.

Members also noted a pre-meeting comment from XXXXX advising that XXXXX was continuing to seek information from XXXXX member constituents, and if necessary would provide additional comment through XXXXX.

In discussing whether to proceed with a scheduling decision at this Meeting the Committee:

- Noted that it appeared that the cosmetics industry was complying with requirements of the current EU limits, so there would be little impact on this group of products.
- Noted a Member's opinion that the issue driving lower cut-offs for scheduling should be skin sensitisation as the data regarding carcinogenicity risk was not strong.

- Noted that the PEC report used "free formaldehyde" when stipulating cut-off concentrations, while the current scheduling of paraformaldehyde and formaldehyde refer to "formaldehyde". A Member proposed, and Committee agreed, that any scheduling decision should adopt use of "free formaldehyde" as this more clearly reflects the risk being addressed by scheduling.
- Noted advice indicating anecdotal evidence of non-cosmetic product manufacturers having concerns about their ability to reduce free formaldehyde levels to ≤ 0.2%.
- Noted that formaldehyde may be used in human medicines at levels below the current 5% cut-off yet > 0.2%. A Member asserted that if the sensitisation risk at > 0.2% was of concern for cosmetics, then perhaps medicines with this concentration should be retained in Schedule 2 instead of exempted.
- The Committee generally agreed that dropping the exemption cut-off from 5% to 0.2% for non-cosmetic domestic use products could have a large regulatory impact, as could a similar move for medicines in Schedule 2.
- The Committee therefore agreed to foreshadow consideration at the October 2007 NDPSC Meeting to allow time to obtain information about formaldehyde in medicines, and for stakeholders to comment – particularly should there be impact on a non-cosmetic domestic use that the Committee had overlooked.
- In aiding this consultation the following preliminary draft of amendments reflected the majority of suggestions from the Member's discussion. However, Stakeholders are advised that the October 2007 NDPSC consideration will not be limited in any way to these drafts.

<u>Some preliminary draft formaldehyde amendments to assist stakeholder consultation (drafts only and do not define or limit the scope of the October 2007 consideration). Entries would be mirrored for paraformaldehyde.</u>

Schedule 2 – Draft Amendment

† FORMALDEHYDE (excluding its derivatives) for human therapeutic use **except**:

(a) in oral hygiene preparations containing 0.1% or less of free formaldehyde; or

(b) in other preparations containing 0.2 per cent or less of free formaldehyde.

Schedule 6 – Draft Amendment

† FORMALDEHYDE (excluding its derivatives) **except**:

(a) for human therapeutic use;

(b) in oral hygiene preparations containing 0.1 per cent or less of free formaldehyde;

(c) in nail hardener cosmetic preparations containing 5 per cent or less of free formaldehyde;

(d) in all other non-aerosol cosmetic preparations containing 0.2 per cent or less of free formaldehyde; or

(e) in all other non-cosmetic preparations containing 0.2 per cent or less of free formaldehyde.

Appendix C – Draft New Entry

FORMALDEHYDE in aerosols for cosmetic use.

OUTCOME

The Committee:

- Agreed to foreshadow consideration at the October 2007 NDPSC Meeting of the scheduling of formaldehyde and paraformaldehyde, to allow a broadening to all use patterns (include human therapeutic use and non-cosmetic domestic use) rather than just those stipulated in the NICNAS formaldehyde PEC Assessment Report (cosmetic use).
- Strongly encouraged stakeholders, particularly those with an interest in these broader use patterns (human therapeutic use and non-cosmetic domestic use) to submit pre-meeting comments for the October 2007 NDPSC Meeting.

8. OTHER MATTERS FOR CONSIDERATION

Nil items.

9. INFORMATION ITEMS (AG/VET, INDUSTRIAL & DOMESTIC CHEMICALS)

Nil items.

PHARMACEUTICALS

10. MATTERS ARISING FROM THE MINUTES OF THE PREVIOUS MEETING (CONSIDERATION OF POST-MEETING SUBMISSIONS UNDER 42ZCZ)

10.1 ORLISTAT

PURPOSE

The Committee considered post meeting comments about the decision to remove the Appendix H listing of orlistat.

BACKGROUND

At the February 2006 NDPSC Meeting, the Committee considered an application from XXXXX to include orlistat in Appendix H of the SUSDP. The Committee noted additional information on a post-marketing surveillance study, media survey and consumer/market research, as well as the experience gained by pharmacists in screening and consulting patients on the suitability of orlistat for other conditions. The Committee also believed that the newly amended Therapeutic Goods Advertising Code (TGAC) which had been strengthened with regards to the advertising of weight loss products would ensure responsible and appropriate branded advertising of XXXXX orlistat XXXXX by the sponsor. The Committee hence agreed to include orlistat in Appendix H on the grounds of potential public health benefit (Decision 2006/46-29). This decision was confirmed at the June 2006 Meeting.

At the October 2006 NDPSC Meeting, the Committee considered the media attention which had been focused on the direct-to-consumer advertising of the orlistat XXXXX. At this time the Committee also considered a submission from XXXXX which requested the Committee review the scheduling and Appendix H listing of orlistat. After discussion of these issues the Committee agreed to foreshadow consideration of the scheduling and Appendix H listing of orlistat for the February 2007 Meeting.

The February 2007 NDPSC Meeting considered the scheduling and Appendix H listing of orlistat. After lengthy discussion and consideration of the evidence put before it, including advice from professionals and consumers that direct-to-consumer advertising increased pressure on pharmacists to provide orlistat to consumers, the Committee decided that, on balance, there was insufficient public health benefit associated with allowing direct-to-consumer advertising of orlistat as it was indicated for use in a relatively small group of patients, not for the general population who might wish to manage more minor weight issues. This advertising had the potential to result in inappropriate patterns of use in patients for whom orlistat was neither indicated nor appropriate. Further, the Committee also decided that retaining orlistat in Schedule 3

would ensure that it remained available for appropriate patients with professional advice from pharmacists.

DISCUSSION

The Committee discussed the provisions of Section 52E (S52E) of the *Therapeutic Goods Act 1989* (the Act) and considered those matters referred to in subsection 52E(1) which were relevant to the consideration of the Appendix H listing of orlistat. The Committee also discussed the provisions of the NCCTG's guidelines on Appendix H advertising and noted that, while these were of a lower order of importance than the Act, they were relevant to the consideration and worked to support the provisions of S52E. The Committee noted, however, that some of these matters set down in S52E carried a greater weight of relevance than others in this consideration.

Members reflected on precisely what they were considering: whether it was only the Appendix H listing of the substance or also the Schedule 3 status of the substance, as there were a number of post-Meeting submissions relating to the Schedule 3 status of orlistat. A Member felt that it should only be the Appendix H listing of orlistat as no change had been made to the scheduling status of the substance. Another Member contended that the change to Appendix H listing was effectively a change to the scheduling status of the substance, therefore all post-Meeting comments should be considered and that this would provide natural justice to all parties. The Committee noted that the pre-Meeting gazette notice for the February 2007 Meeting was for 'Consideration of the scheduling status of orlistat' and, therefore, felt that all of the post-Meeting submissions, whether they related to the Appendix H listing or Schedule 3 status, should be considered by the Committee.

The Committee recalled the following matters from the February 2007 NDPSC meeting:

- XXXXX had reported feedback from XXXXX that advertising of orlistat, as a consequence of Appendix H listing, had put extra stress on pharmacists through patients arriving with the expectation of being given the substance. A Member had stated that such patient expectations made it more difficult for pharmacists to engage in a proper clinical discussion with the patient.
- Members felt that, given the restricted indications for use of orlistat and the fact that the patient group falling within these indications was small, advertising of such a substance would potentially lead to inappropriate patterns of use in patients for whom orlistat was neither indicated nor appropriate.

Thirty-three post-meeting form letters from pharmacists were received with regard to the February 2007 orlistat Appendix H decision. Another 607 of these form letters were received as part of XXXXX post-Meeting submission on this matter. It appears that these may have been circulated by XXXXX to XXXXX members. Whilst these letters were not valid submissions as set down in 42ZCZ of the *Therapeutic Goods Regulations 1990* (the

Regulations), the Committee agreed to consider them. Members particularly noted the following:

- Advertising orlistat prompts consumers to visit their pharmacy, speak to their pharmacist and become involved in the management of their medical conditions. It informs the public of the availability of a safe medicine which is the only one in the over-the-counter weight loss field which has been clinically proven to work. Restricting this advertising would lead to fewer people, for whom orlistat is appropriate, seeking advice from their pharmacist.
- Pharmacists and pharmacy staff have been well educated and trained in the use of orlistat and, overall, have handled the use of the substance well.
- Pharmacists pledged that they would provide adequate counselling and information to customers for whom orlistat is appropriate. The Committee noted that the February decision to retain orlistat in Schedule 3 demonstrated its faith in pharmacists that they were already doing so.

XXXXX provided a post-Meeting comment calling for the Appendix H status of orlistat to be reinstated. XXXXX main points were:

- Orlistat had been advertised for only three weeks before all advertising was withdrawn, therefore no reasonable comparison had yet been made regarding the risks of advertising outweighing the benefits of it. Assessing the public health impact of this advertising would take longer than the actual period of advertising of the substance.
- The Appendix H listing for orlistat had been revoked due to the deficiencies in supply of the substance by some pharmacists, not because of any concerns about safety or efficacy. The Committee recalled that the February decision was not made because of the actions of some pharmacists, but because, on balance, there was insufficient public health benefit. XXXXX pointed out that orlistat is a clinically proven safe and effective treatment for weight loss (a point never refuted by the Committee) and by making the decision to remove Appendix H listing, XXXXX was of the opinion that the Committee had not acted in the interest of public health.
- XXXXX quoted figures from the NHMRC's *Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults* which in 1999- 2000 showed that approximately 67% of adult males and 52% of adult females were classified as overweight or obese. These guidelines define obesity as a BMI > 30 and overweight as a BMI > 27. XXXXX noted that although not all overweight people have risk factors, many of them would have and, therefore, are appropriate for orlistat. The Committee noted that orlistat is only indicated for those with a BMI between 27 and 30 if they have co morbidities (i.e., that it is not indicated for all overweight adults). Given these numbers, XXXXX felt that the Committee's conclusion that orlistat was indicated only for a small group of people was incorrect and by removing Appendix

H listing, a significant number of people had been prevented from being informed about orlistat.

- XXXXX disagreed with the statements the Committee made about long term safety of orlistat not being established and that it has significant long term risk of increasing age-related macular degeneration (ARMD). A four year study, evaluated by TGA and included in the PI (XENDOS) had shown that orlistat was safe long term. Regarding ARMD, this was a theoretical issue which had been reviewed by ADRAC and about which XXXXX had only received one report worldwide (out of XXXXX patient exposures) as of 15 November 2005. XXXXX stated that given this, it was unlikely there was a causal link between orlistat and ARMD. XXXXX also noted that it was not required that all side effects be listed in all forms of advertising. While the Committee accepted this point made by XXXXX, it was recalled by the Committee that the long term risk of ARMD and the need to mention this along with other side effects was a point raised by XXXXX and not necessarily endorsed by the Committee.
- Data soon to be published at the European Conference of Obesity further highlighted orlistat's ability to reduce cardiovascular risk and improve the weight loss outcomes of appropriate individuals. XXXXX stated that, despite this clinically proven efficacy, orlistat advertising has been revoked while other, unproven treatments were still permitted to be advertised. The Committee noted that, while this may be the case, it only has control over the advertising of those substances listed in Schedule 3 of the SUSDP.

XXXXX provided a post-Meeting comment asking the Committee to reconsider the scheduling of orlistat from Schedule 3 to Schedule 4. Most of this post-meeting comment responded to points in the Record of Reasons made by other public commenters. XXXXX did provide responses to a number of points the Committee made. These points were:

- Regarding the Committees' comment that XXXXX should have referred the matter of pharmacists not following the guidelines to the Pharmacy Board of NSW (PBNSW), XXXXX stated that XXXXX had written to PBNSW regarding this and XXXXX concerns that other Schedule 3 substances may be being dispensed inappropriately. XXXXX had also asked PBNSW what measures would be instituted to ensure this did not continue to happen.
- XXXXX addressed the Committee's concern that XXXXX may have chosen the pharmacies XXXXX tested because XXXXX had information on them undertaking questionable practices. XXXXX stated that none of the pharmacies or pharmacists dispensing practices was known to XXXXX. Further, XXXXX stated that XXXXX are an independent, not-for-profit organisation which receives no funding from government or industry and that XXXXX would undertake no practices which may undermine XXXXX credibility.

- XXXXX agreed with the Member who stated that the issue of orlistat scheduling needed to be viewed with fresh eyes. XXXXX also agreed with the point made about Schedule 3 medicines not being used for medical diagnosis or management of serious conditions and the fact that many of these patients do have such co-morbidities which do require medical management. XXXXX stated that for these patients it is counselling and longer term care which lead to sustainable outcomes and result in long term weight loss.
- XXXXX reiterated XXXXX point that the guidelines for orlistat as a Schedule 3 medicine were not being followed and it was in the public interest to continue to make this product available but to limit use to a subset of the population which fitted the clinical profile of the drug.

XXXXX provided a post-Meeting comment in which XXXXX called for the Committee to set aside their decision regarding the Appendix H listing of orlistat. XXXXX reiterated the points that were made in XXXXX submission to the February 2007 NDPSC Meeting and made some further statements. XXXXX main points were:

- There was no sign that the information from "professionals and consumers" [here XXXXX were quoting from the February 2007 RoR, page 177] regarding the increased pressure on pharmacists to provide orlistat had been tested for scientific validity and the information was presented without reference to any evidence being provided from the professionals regarding this matter.
- XXXXX stated that if this pressure on pharmacists had lead to inappropriate patterns of medicine use, then the Committee had to assume that pharmacists were incompetent at managing their role of allowing patients access to Schedule 3 medicines. Again, the Committee reiterated that the February decision demonstrated that the supply of orlistat as a S3 medicine remained appropriate.
- The appropriateness and lawfulness of advertisements was a matter which should be addressed under the *Therapeutic Goods Advertising Code* and *Therapeutic Goods Regulations 1990,* not by the NDPSC.
- There was no indication in the decision made by the Committee as to how the "balance" was struck for the Committee to conclude there was "insufficient public health benefit" and that there was no indication made of what a "significant" public health benefit may be. XXXXX stated that, given the obesity crisis, even some public health benefit was worth supporting and the balance between inappropriate patterns of use and the need for greater public awareness of treatments for obesity needed to be weighted on the side of the latter.

XXXXX provided a post-Meeting comment in which XXXXX stated that it was not in the public health interest to allow unproven weight loss aids to be advertised and clinically proven ones not to be. Again, the Committee noted that it had no control over the advertising of non-Schedule 3 therapeutic goods. XXXXX reiterated the points that

were made in XXXXX submission to the February 2007 NDPSC Meeting and address some of the Appendix H inclusion guidelines. XXXXX main points were:

- Potential public health benefit – Figures from the Australian Institute of Health and Welfare (AIHW) were quoted showing that 67% of males and 55% of females are overweight or obese. This was equated to 40% of all adults being overweight (5.4 million, 3.2 million of which have a BMI of 27 – 29) and 20% being obese (2.7 million). XXXXX stated that if half the overweight patients with a BMI of 27 – 29 have co-morbidities this meant, conservatively, there were 1.6 million overweight patients and 2.7 million obese patients for whom orlistat was indicated.
- Advertising leading to inappropriate patterns of use – inappropriate patterns of use is usually interpreted as abuse or misuse (the Committee noted that abuse is a separate provision under S52E), not use outside indications and, if use outside of indications is interpreted this way, would this mean the consumer would suffer harm? XXXXX stated that clinical data had shown that there appeared to be a lack of efficacy in patients with a BMI under 27, thus the risk associated with use outside the indication may be that such use does not result in weight loss. Further, there were no serious adverse events reported with orlistat, therefore the risk of harm was low. XXXXX also noted that there were a large amounts of listed weight loss medicines available in Australia which may be advertised but have no clinical proof of efficacy. XXXXX provided details of these medicines and stated that there seemed to be inequalities in the area of advertising of weight loss products. They suggested that the lack of advertising of orlistat means that patients would only hear of listed weight loss medicines and that this may be considered an inappropriate pattern of medication use due to them targeting all consumers, not just those with a BMI greater than 27. Again, the Committee accepted this point but noted that it had no power over the advertising of such products.
- The requirements to comply with the TGAC – the advertisement which was subject to complaint had been approved by XXXXX, thus the sponsor had grounds to believe their advertisement complied with the TGAC.
- Responsibility of pharmacists to be actively involved in supply of the substance – XXXXX noted the Committees' referral of its concern regarding pharmacists not complying with guidelines to the PBNSW. XXXXX stated, however, that the sample of 30 pharmacies did not seem large enough to judge the behaviour of the entire profession and presented 607 pledges from pharmacies stating that they follow the required guidelines for supply of orlistat. Again, the Committee noted that its decision to retain in Schedule 3 demonstrated that the Committee did not have issue with orlistat being appropriately supplied by pharmacists without a doctor's prescription. XXXXX stated that there was strong feeling that a decision based on the limited amount of evidence presented by XXXXX did not provide a basis for solid, evidence based decision making.

- Availability of CMI and patient education – XXXXX noted that the orlistat CMI was available in the medicine carton and this, and the package labelling, reinforce correct use of the substance.
- The Committee also decided to consider the submissions from XXXXX even though these stakeholders had not provided pre-Meeting submissions as well as considering the other 640 form letters from pharmacists. A number of Members felt that the fact that pharmacists were willing to make such a pledge about adhering to supply guidelines for orlistat was positive and that it showed that pharmacists found the medication a valuable tool and advertising of it helped pharmacists to initiate clinical conversations about weight loss. However a number of other Members stated that adherence to such guidelines was mandatory for the supply of a Schedule 3 substance and that all pharmacists are required to do so whether they had pledged to or not.

A post-Meeting comment was received from the XXXXX after the deadline for such submissions. Members chose to allow consideration of this comment and noted the following:

- XXXXX did not support the listing of orlistat in Appendix H but did support its continued listing in Schedule 3 as it meets all the criteria for a Schedule 3 medicine.
- XXXXX believed that the issue of advertising had become tangled with the issue of the actual scheduling of orlistat. XXXXX stated that the current regulatory systems in place for advertising (TGAC, CRP) were sufficiently thorough in their regulation of direct to consumer advertising and in ensuring the appropriateness of these advertisements. XXXXX stated that despite this, it appeared that a single advertising breach lead the Committee to reconsider and reverse an earlier, apparently well considered decision.

XXXXX stated that, while XXXXX were sure the Committee had considered this issue fully on every occasion, the chain of events related to this consideration may give the impression that the decisions of the NDPSC are easily reversed and also cast doubt on the integrity of such decisions and the process under which they were made.

The Committee considered the difficulty pharmacists some times have in discussing weight loss options with patients was the large number of unproven products on the market. A Member stated that it was difficult to initiate a clinical conversation with patients about weight loss when the patient themselves did not start the conversation. The Member felt that the advertising of orlistat made the patient aware there was a fully evaluated alternative available and that this made it easier for the pharmacist to discuss a proven treatment for obesity with the patient. The Member also stated that the supply of orlistat had very rigorous protocols and patient screening criteria in place which helped to direct any discussion with patients and that a number of tools to enable patients to calculate their BMI and initiate a discussion with the pharmacist were available. A number of other Members felt that this was of public health benefit. Another Member expressed concern that pharmacists found it difficult to initiate conversations on this issue

with patients and stated that general practitioners might have an easier time initiating such a conversation with their patients.

A Member stated that, in their opinion, there was little evidence of inappropriate use of the substance which had been presented to the Committee. The Member also stated that there was clinical evidence that even if a patient with a BMI of less that 27 used the product, they would be unlikely to lose any weight. The Member contended that this meant that even if a patient with a BMI under 27 did buy the product they would probably only do so once and, therefore, there would be no harm done by inappropriate use of the substance. Another Member reminded the Committee that there had been some anecdotal evidence presented to the February 2007 Meeting of inappropriate supply of orlistat to patients. There were concerns aired that there were risks from inappropriate use for patients taking the substance outside its indications as the patient would be receiving no benefit from the substance but exposing themselves to potential adverse events. A Member postulated that if the patient had any body image issues but was outside the indications for use, their ability to purchase orlistat may serve to reinforce these issues, again exposing the patient to risk without any benefit. On balance, the Member felt that any benefit to public health of listing orlistat in Appendix H was outweighed by the risks of doing so. Another Member suggested that even a 10% weight loss was of benefit to patients and that direct-to-consumer advertising helped to facilitate this. Members agreed that there was benefit to weight loss *per se* but a Member felt that this was the case regardless of whether or not there was direct-to-consumer advertising.

A Member noted that the February decision was based partly on the number of patients that orlistat was indicated for and that the Committee had now been presented with evidence that the number may not have been as small as initially thought. Another Member agreed that this was the case and that the statistics presented in some submissions showed that the number of patients that orlistat was indicated for was much larger than the Committee originally might have considered.

A Member noted that there were opposing views on the advertising of Schedule 3 medicines presented by XXXXX. A Member noted that the other professional bodies, such as XXXXX submissions from the February 2007 Meeting also stated opposition to the Appendix H listing of orlistat. Another Member reminded the Committee that it had been presented with over 640 form letters which stated that pharmacists were adhering to supply guidelines and the evidence presented on inappropriate use had been anecdotal. The Member contended that this showed that a great number of pharmacists were sufficiently motivated to make a comment in writing and that the majority supplied the substance properly. A Member stated that there was a difference between pharmacists signing a form letter and actually going out and testing their practice in a real world setting and that there had been some evidence that the guidelines were not being adhered to. Another Member stated that there was information in the documentation presented to the Committee that pharmacists were better at dealing with symptom-based requests and that this was backed up by the results of a report done by Dr Benrimoj from the

University of Sydney (Benrimoj *SI, A Cost-Benefit Analysis of Pharmacist Only (S3) and Pharmacy Medicines (S2) and Risk-Based Evaluation of the Standards*, Faculty of Pharmacy, The University of Sydney, June 2005) which stated that, at the level of individual patient care, pharmacies were able to show good levels of compliance with protocols for symptom based requests for assistance but lower rates of compliance with respect to product requests. Another Member stated that the results from the Benrimoj study needed to be put into perspective as, for the product vs. symptoms based questions, they were only graded on the terms 'unsatisfactory', 'satisfactory' or 'excellent' and there was not a great deal of difference between the results. The Member stated that while the results showed that, for product requests, pharmacists were slightly less able to intervene as a patient had likely already made a decision, the fact that there was still an intervention was of benefit to the patient. The Member also noted that orlistat has had more training surrounding its supply that any other Schedule 3 substance.

A Member suggested that if patients had a co-morbidity then they should be under the supervision of a doctor for their treatment of both their weight loss issue and co-morbidities. However, the Member felt that the objections raised about direct-to-consumer advertising could be answered by non-branded advertising as it would encourage patients to interact with their pharmacist about weight loss issues without putting pressure on the pharmacist to prescribe a particular substance. Another Member stated that this view was supported by XXXXX other submission relating to the guidelines for the branded advertising of Schedule 3 substances which stated that branded advertising can lead to undue pressure on pharmacists.

A Member stated that in looking at the benefits and risks, the Committee needed to consider what benefit over and above Schedule 3 inclusion the Appendix H listing of orlistat provided. The Member stated that by placing the substance in Schedule 3, the benefit to the community through ease of access was increased but was concerned that the Appendix H inclusion had only increased the risk to consumers, not the benefit. Another Member stated that the benefit to Appendix H listing was marginal. A Member re-emphasised the fact that orlistat was only advertised for three weeks before advertising was withdrawn and stated that the outcome of the complaint made to the CRP pointed more to a failure of the advertising system, not the scheduling of orlistat. It was acknowledged by the Committee that the fact that the system allowed for the existence of the CRP showed that there are checks and balances in place. A Member agreed that the Committee had probably been given no real information about the impact of the brief period of advertising of orlistat had on patient behaviour. The Member also pointed out that the Committee had only seen results from XXXXX survey and that this survey used only a small sample of pharmacies. A Member stated that a more statistically robust test of pharmacist dispensing behaviours would be of benefit to the Committee.

A Member noted that with regards to the toxicology of the substance there had been certain issues (ARMD, vitamin deficiency and faecal incontinence) that the Committee had been concerned about when making the February 2006 decision and that the

Committee had been reassured that these would be addressed in the PI and CMI and advertising for orlistat. The Member noted that concerns about ARMD had been addressed, however the other two concerns had not been addressed. The Member stated that these issues were still of concern, that neither were being drawn to the attention of consumers through advertising and that they did need to be addressed, even though the toxicological profile of orlistat is relatively safe. Another Member stated that the PI and CMI do mention vitamin deficiency and faecal incontinence and that these are also mentioned on the product label, thus consumers are made aware of these risks. Another Member stated that faecal incontinence is a highly predictable side effect which pharmacists know to counsel patients about and that patients will modify their diets if they suffer this side effect. A Member stated that that the Committee had accepted that risk/ benefit profile for orlistat fit the criteria of a Schedule 3 medicine. A Member stated that the product information also talked about stopping treatment if the patient had not lost a certain amount of weight in a certain period of time.

A Member stated that a critical element in the February 2006 decision to grant Appendix H listing for orlistat was the fact that the TGAC had been strengthened in such a way as to ensure that orlistat would not be advertised to inappropriate patient populations. The Member stated that the CRP complaint which was upheld suggested that this had not actually been the case. It was noted that, while the Committee has the requirement under the NCCTG guidelines to consider the provisions of the TGAC, the matter of specific advertisements and caveats on these was the purview of the TGACC and was separate to the NDPSC's consideration of an issue.

Another Member stated that the Committee had felt that the advertising of orlistat could only raise awareness of the issue and that it would help the pharmacist begin a dialogue with the patient, not just make the patient aware of the product and leave them to make their own decision. The Member felt that the benefit of this interaction with the pharmacist about the issue outweighed any potential risk.

A Member noted that the February 2007 Minutes referred to data being submitted by XXXXX regarding the pressure that direct-to-consumer advertising was putting on pharmacists, but felt that it should be acknowledged that the information described in XXXXX submission was feedback from XXXXX rather than actual data *per se*.

The Committee was reminded that pharmacotherapy for weight loss should perhaps only be considered after diet, exercise and other behaviour modifications had been looked at. The Member felt that this message (i.e., that pharmacotherapy was not a first line treatment) was not going to come across in any branded advertising of orlistat to the public and, thus, an appropriate balance between benefit and risk would not be able to be achieved as it would have an adverse effect on the extent and patterns of use of the substance. A Member stated that if pharmacists were following the supply protocols, then they would be advising patients that orlistat was not a first line therapy for weight loss and discuss with them diet and exercise modifications. Another Member noted that the flow chart from the XXXXX protocol did not mention these factors, but that the flow

chart listed “receive request for orlistat”, “clarify patients’ need”, “confirm orlistat is appropriate”, “supply orlistat.” Another Member stated that the “clarify need” section of the chart was where the conversation regarding other ways of reducing weight would happen. A Member noted that there was no explanation in the protocol to pharmacists to discuss diet and exercise as part of this. Another Member stated that this extra information was in the training pharmacists received. Another Member noted that in the flow chart, after the “supply” orlistat, there was information for the pharmacist to counsel the patient on matters including side effects, interactions, vitamin supplementation and lifestyle modification. A Member stated that there are differences between protocols and expectations and what actually happens in practice.

Members discussed XXXXX request for the rescheduling of orlistat to Schedule 4, given the current indications for orlistat are for obesity or for patients with co-morbidities which would be managed by a doctor. A Member noted that this was discussed at the February 2007 Meeting, as were the criteria for Schedule 3 inclusion. The Member noted that one of the criteria of the NDPSC guidelines for Schedule 3 medicines was that the indications for use be for an ailment which is amenable to short-term treatment or capable of being monitored by the consumer with assistance from a pharmacist. The Member stated that, for the patients for whom orlistat is indicated, whether short-term treatment was possible or appropriate and whether their condition could be adequately monitored by a pharmacist was a relevant consideration. The Member noted that a number of other Members had raised points that alluded to the fact that there were difficulties in the long-term monitoring and maintenance of obesity and associated co-morbidities and, thus, questioned whether Schedule 3 was appropriate for orlistat. Another Member noted that pharmacists were generally unable to screen for the majority of co-morbidities which patients may have. A Member noted that patients commencing treatment with orlistat were advised to let their doctor know they were taking the medication. The Member also stated that many of the patients with co-morbidities were seeing their doctor regularly for treatment of these conditions. Another Member stated that the orlistat protocols referred to weight loss as being a long term or lifelong strategy with regular reviews being required and that, therefore, perhaps these protocols were in conflict with the requirements of scheduling a Schedule 3 medicine. A Member stated that the Committee was not there to debate the appropriateness of a protocol, however another Member stated that the issue of short-term treatment was crucial in deciding whether a substance belonged in Schedule 3. Another Member stated that there were a number of other substances in lower schedules such as aspirin as an anticoagulant which were indicated for long-term treatment of conditions. Furthermore, beta agonists for the treatment of asthma, nitrates for angina and corticosteroids for allergic rhinitis were all examples of Schedule 3 medicines indicated for the treatment of chronic conditions so, although one of the criteria in the guidelines states that treatment should be for short-term conditions, a precedent had clearly been set.

OUTCOME

The discussion of the Committee's considerations of the scheduling of orlistat were summarised by the Chair and the arguments put forward under Section 52E of the *Therapeutic Goods Act 1989* were as follows:

- that direct-to-consumer advertising of orlistat had the potential to lead to inappropriate extent and patterns of use of orlistat outside its registered indications;
- that direct-to-consumer advertising of orlistat may adversely affect the ability of pharmacists to provide advice about other appropriate weight management strategies;
- that there were concerns about the ability of direct-to-consumer advertising of orlistat to accurately present information about the potential toxicity, safety, risks and benefits of orlistat and the specific indications for use;
- that while acknowledging the need to address the problems of obesity in the Australian community, pharmacotherapy was not the first line of treatment for weight management and direct-to-consumer advertising of orlistat had the potential to over-emphasise its role over those of lifestyle change;
- that the safeguards that allowed inclusion in Schedule 3, such as education programmes for pharmacists and consumer information, did not remove the potential for direct-to-consumer advertising of orlistat to adversely affect appropriate provision of orlistat;
- that the changes to the wording of the Therapeutic Goods Advertising Code (TGAC) aimed at strengthening the requirements of advertising weight loss products had not sufficiently prevented messages promoting inappropriate use of orlistat and the Committee did not feel that the current TGAC was able to prevent advertising from over-emphasising the role of pharmacotherapy.
- On balance, the NDPSC believed that the potential for direct-to-consumer advertising of orlistat to lead to inappropriate patterns of use worsened the risk-benefit balance of access to the substance and the committee felt it necessary to protect public health by preventing direct to consumer advertising of this product.

For all of these reasons the Committee confirmed the February 2007 NDPSC decision (2007/49-17) to remove orlistat from Appendix H of the SUSDP.

The Committee also decided that the risk/ benefit of orlistat (in the absence of direct-to-consumer advertising) remained appropriate for Schedule 3 due to the need to provide ready access to this medicine which has been provided by pharmacists for three years without significant safety concerns or incidence of ADRs that would require inclusion in Schedule 4.

In reaching this decision, the NDPSC considered the representations from peak professional associations, State and Territory pharmacy boards and peak consumer organisations such as XXXXX, that all argued strongly against direct-to consumer

advertising of orlistat on the grounds that it led to inappropriate dispensing pressure on pharmacists and had the potential to mislead consumers.

Full consideration was given to the XXXXX, which highlighted the prevalence of obesity in the Australian population, the safety profile of orlistat, the short period of direct-to-consumer advertising of orlistat that had occurred before it was ordered by the Complaints Resolution Panel to remove its advertisements, and the education material that is provided by pharmacy. Similar views were covered in XXXXX submission which was also considered in detail.

The NDPSC also considered the views of XXXXX supporting the Appendix H listing of orlistat. XXXXX submission again highlighted the current obesity problem in Australia and the educational materials provided by pharmacy. The NDPSC noted an additional contrasting submission from XXXXX relating to the item (1.7.1.4) on Appendix H listing that was critical of branded advertising of Schedule 3 substances due to its effect on the ability of the pharmacist to provide the best professional advice to consumers.

The NDPSC considered the XXXXX submission which highlighted the potential for the inappropriate supply of orlistat via pharmacists and argued for Schedule 4 listing of orlistat. The Committee discussed these concerns in detail, but agreed that the need for access, the safety profile and the professional interaction at the pharmacist level was appropriate for Schedule 3 listing.

In summary, after considering all post-meeting submissions, the NDPSC decided to confirm its February 2007 decision to revoke the Appendix H listing as per the relevant matters listed in S52E of the Act and according to the NCCTG Guidelines on Branded Advertising of Schedule 3 Medicines, it was not appropriate for orlistat to be advertised direct-to-consumers.

Further to this the Committee discussed amending the current implementation date of 1 September 2007 for this decision. The Committee decided that, given the time frame of the current legal proceedings, the implementation date of this decision should be delayed by one month to 1 October 2007.

10.2 VITAMIN A

PURPOSE

The Committee considered post-Meeting comments about the scheduling of vitamin A.

BACKGROUND

The October 2006 TTHWP meeting endorsed the recommendations and actions in relation to each medicine listed in Table 3 “Deferred harmonisation proposals” from the June 2006 NDPSC Meeting, including actions for vitamin A and selenium. The TTHWP

agreed that these actions would be tabled for consideration at the February 2007 NDPSC Meeting to allow appropriate public consultation.

The February 2007 NDPSC Meeting considered the scheduling of vitamin A with a view to harmonising the scheduling of these substances between Australia and New Zealand. The Committee agreed to:

- harmonise the scheduling of vitamin A for internal use with New Zealand on the basis of the established upper level of intake per day of vitamin A;
- recommend to New Zealand that they harmonise with Australia on topical preparations of vitamin A because topical preparations containing 1% or less are not teratogenic and;
- adopt Retinol Equivalents as units of measurement for vitamin A as per NHMRC recommendations.

DISCUSSION

A post-Meeting comment was received from XXXXX. As XXXXX did not put forward a submission to the February 2007 NDPSC Meeting this was not a valid post-meeting comment, however the Committee chose to consider it. The Committee noted the following:

- XXXXX sought confirmation from the Committee that using the units International Units (IU) on product labelling would be acceptable. [Labelling of products is approved by TGA and is not an issue for the NDPSC]. Further, XXXXX suggested that the proposed amendment be expressed as both mcg Retinol Equivalents (RE) and IU.

XXXXX noted that the proposed amendment did not make mention of the potential for toxicity with vitamin A, especially in pregnancy. The Committee discussed the fact that there is a requirement in RASML for all products containing vitamin A to have the warning “If you are pregnant, or considering becoming pregnant, do not take vitamin A supplements without consulting your doctor or pharmacist”.

The XXXXX provided a post-Meeting comment regarding the vitamin A considerations from the February 2007 NDPSC Meeting. XXXXX main point was:

- The labelling requirements for the Required Advisory Statements for Medicine Labels (RASML) will need to be updated to reflect the change from IU to mcg RE. The Committee noted that the RASML was notified of this change in early April 2007. Further, due to this change in units of expression the XXXXX requested that industry be given at least 18 months to implement these changes.

A late post-Meeting comment was received from XXXXX outlining concern that the proposed schedule entry for vitamin A did not make reference to warning statements of the use of the substance in pregnancy or in high doses and asked that the Committee

consider this issue. XXXXX also raised concern that the proposed entry made no differentiation between the maximum daily dose for adults and children. XXXXX noted that the current upper level of intake (ULI) for vitamin A in children aged 4 – 8 years is 900µg RE/ day, for children 9- 13 is 1700 µg RE/ day and for children aged between 14 and 18 is 2800µg RE/ day. The Committee noted that the current S4 entry for vitamin A refers to a maximum daily dose for adults, but not children. XXXXX requested that the Committee consider whether it was appropriate to alter the cut-off in the proposed entry to distinguish between adults and children.

A Member stated that by including reference to RASML in the schedule entry, this would make it clear to manufacturers that they were required to comply with the provisions of the document. The Committee discussed this but noted that the labelling requirements under RASML would be referred to in the introduction of the SUSMP and that compliance with RASML was already a requirement for any medicine listed by the TGA.

A Member stated that the requirement for daily doses was not mentioned in the proposed schedule entry. It was noted that the amount of vitamin A in the proposed schedule entry was taken from the NHMRC recommendations discussed at the February 2007 Meeting and the Committee considered whether it would be reasonable to include reference to a maximum daily dose of vitamin A in the schedule entry, given the concerns around toxicity and foetal malformation with overdose of the substance.

Members discussed whether an exemption should be granted to allow the implementation of new labelling for affected products, however it was felt that the new schedule entry did not preclude labels from referring to both IU and micrograms RE and, as some products would have to be re-labelled anyway to allow for the raised limits of vitamin A, that such an exemption was not required.

DECISION 2007/50 – 8 (Variation of Decision 2007/49-3)

The Committee agreed to vary the February 2007 NDPSC decision (2007/49-3), namely to harmonise the scheduling of vitamin A for internal use with New Zealand, to recommend that New Zealand adopt the scheduling of vitamin A for topical use and to adopt Retinol Equivalents as the units of measurement for vitamin A, by including a maximum daily dose of 3000 micrograms retinol equivalents or less in the entry. This maximum is consistent with the upper level of daily intake of vitamin A.

Schedule 4 – Amendment

VITAMIN A – Amend entry to read:

VITAMIN A for human therapeutic or cosmetic use **except**:

(a) in preparations for topical use containing 1 per cent or less of vitamin A;

(b) in preparations for internal use containing 3000 micrograms retinol equivalents or less of vitamin A per daily dose; or

(c) in preparations for parenteral nutrition replacement.

10.2.2 SELENIUM

PURPOSE

The Committee considered post-Meeting comments about the decisions made on the scheduling of selenium.

BACKGROUND

The October 2006 TTHWP meeting endorsed the recommendations and actions in relation to each medicine listed in Table 3 "Deferred harmonisation proposals" from the June 2006 NDPSC Meeting, including actions for Vitamin A and selenium. The TTHWP agreed that these actions would be tabled for consideration at the February 2007 NDPSC Meeting to allow appropriate public consultation.

The February 2007 NDPSC Meeting considered the scheduling of vitamin A and selenium with a view to harmonising the scheduling of these substances between Australia and New Zealand. For selenium the Committee agreed to:

- as per decision 11/2 of the TTHWP, to adopt a cut-off to exempt preparations for internal use containing 150 mcg or less selenium per daily dose; amend the Schedule 2 entry to include internal use preparations containing 150-300 mcg/day selenium; amend the Schedule 4 entry to include internal use preparations containing more than 300 mcg/day selenium;
- as selenium sulfide is the least toxic of the selenium salts and 3.5% selenium sulfide is equivalent to 2.5% elemental selenium, recommend to New Zealand that they adopt the Australian scheduling for topical selenium agents.

DISCUSSION

A post-Meeting comment was received from XXXXX As XXXXX did not put forward a submission to the February 2007 NDPSC Meeting this was not a valid post-meeting comment, however the Committee noted the following:

- The current scheduling made the distinction between organic and inorganic selenium however the proposed scheduling did not. Clarification was sought that the limit proposed is irrespective of the selenium salt used. The Committee recalled that the distinction between organic and inorganic selenium in the schedule entries was first made at the February 1999 NDPSC Meeting in order to bring the Schedule in line with the ANZFA Standard which restricted the amount of selenium in supplementary

sports foods. This decision was seen as providing an appropriate link between selenium in food and in therapeutic goods. The ANZFA Standard made the distinction between organic and inorganic forms of selenium. The ANZFA rationale for this distinction was based on uptake studies which showed that inorganic selenium was absorbed from the gut at a rate of approximately 60% while organic selenium had an uptake rate of 95-98%, however there was little difference in the toxicity of the two forms.

- The current labelling requirements for selenium containing Listable Goods states that products must contain a warning *"This product contains selenium which is toxic in high doses. A daily dose of 100mcg of selenium from dietary supplements should not be exceeded. Selenium containing products are not suitable for use by children under the age of 15 years."* XXXXX wished the Committee to comment on the acceptability of this warning given the increase in the recommended daily dose to 150mcg. The Committee noted that the RASML secretariat has been notified of this change to selenium cut-offs.

XXXXX provided a post-Meeting comment regarding the selenium considerations from the February 2007 NDPSC Meeting. XXXXX main points were:

- XXXXX noted that the new wording of the selenium schedule entry did not distinguish between organic and inorganic forms. XXXXX therefore sought clarification whether the proposed limit was intended to apply irrespective of which form of selenium was used.
- XXXXX also noted the same incongruity between the proposed 150mcg daily dose of selenium and the labelling requirement which states "*This product contains selenium which is toxic in high doses. A daily dose of 100mcg of selenium from dietary supplements should not be exceeded."* XXXXX sought the Committees' advice on how this matter was to be addressed.

A Member noted that, as the schedule entry was for elemental selenium, it did not matter whether the selenium was organic or inorganic. The Member also noted that RASML would pick up any required warning statements. Members agreed that this was the case.

A Member stated that although selenium deficiency has been observed in New Zealand, in Australia it has not and therefore harmonising to New Zealand levels of selenium may not be relevant to Australia. Members discussed this and noted that the selenium levels in the Schedule entries were in line with that stated in the NHMRC guidance document and therefore relevant to both Australia and New Zealand.

A Member noted that the wording in the Schedule 4 entry was not consistently exclusive as the (b)(i) wording referred to '300 mg or less' whereas it should be 'more than 300 mg'. Members agreed that this alteration should be made.

DECISION 2007/50- 9 (Variation to Decision 2007/49-3)

While confirming the Schedule 2 and 3 entries, the Committee varied the February 2007 NDPSC decision (2007/49-3), namely to:

- adopt a cut-off to exempt preparations for internal use containing 150 mcg or less selenium per daily dose;
- amend the schedule 2 entry to include internal use preparations containing 150-300 mcg/day selenium and
- amend the schedule 4 entry to include internal use preparations containing more than 300 mcg/day selenium,

by amending the wording of the Schedule 4 entry to include an 'except'.

Schedule 2 – Amendment

SELENIUM - Amend entry to read:

SELENIUM in preparations for human therapeutic use **except**:

(a) when included in Schedule 4;

(b) for topical use containing 3.5 per cent or less of selenium sulfide; or

(c) in preparations for oral use with a recommended daily dose of 150 micrograms or less of selenium.

Schedule 3 – Amendment

SELENIUM – Delete entry

Schedule 4 – Amendment

SELENIUM - Amend entry to read:

SELENIUM:

(a) for human oral use with a recommended daily dose of more than 300 micrograms; or

(b) for the treatment of animals **except**:

(i) when included in Schedule 6 or 7;

(ii) in solid, slow release bolus preparations each weighing 100 g or more and containing 300 mg or less of selenium per dosage unit;

(iii) in other divided preparations containing 30 micrograms or less of selenium per dosage unit;

(iv) as elemental selenium, in pellets containing 100 g/kg or less of selenium; or

(v) in feeds containing 1 g/tonne or less of selenium.

10.3 RANITIDINE

PURPOSE

The Committee considered post-Meeting comment received in response to the February 2007 NDPSC Meeting decision on the scheduling of ranitidine (Decision 2007/49-22).

BACKGROUND

At the November 2000 Meeting of the NDPSC, the Committee considered a submission to reschedule ranitidine from Schedule 3 to Schedule 2. The Committee discussed the safety profile of ranitidine, including the potential for ranitidine to mask more serious, underlying conditions. The Committee also noted that the indications for the substance were appropriate for a Schedule 2 classification and that the warning statements clearly advised the consumer that the use of the product was for short-term treatment only. Following consideration, the Committee agreed to the inclusion of a new entry in Schedule 2, with retention of Appendix F warning statements, for ranitidine when supplied in packs containing no more than 14 days supply.

The February 2005 Meeting of NDPSC agreed to foreshadow removal of the indication "gastro-oesophageal reflux" from the S2 entry in order to be harmonised with New Zealand on this substance. This recommendation was confirmed at the July 2005 NDPSC Meeting.

The February 2007 NDPSC Meeting considered an application to exempt from scheduling ranitidine 150mg, with a maximum dose of 300 mg/day in packs containing no more than 7 days supply. After consideration, the Committee agreed to amend the scheduling of ranitidine when sold in solid dosage forms in manufacturer's original pack containing not more than 7 days supply with a maximum dose of 300 mg per day from Schedule 2 to exempt from scheduling. The Committee agreed to refer the matter to the Drafting Advisory Panel (DAP) to fine tune the wording of the schedule entries.

DISCUSSION

Members recalled the following from the February 2007 NDPSC Meeting:

- XXXXX submission stated that the product exempt from scheduling would be marketed in packs containing either XXXXX tablets, i.e., XXXXX and the labelling on the package would direct consumers to take one tablet at a time and not take more than two tablets (300mg) in a 24 hour period. The PI and CMI for this product both stated that the maximum daily dose was 300 mg (two 150mg tablets).
- The Committee had concerns regarding exempting oral liquid dosage forms from scheduling. Members agreed that there was potential for liquid dosage forms to be more easily accessed by children and to be used inappropriately (i.e., people drinking straight from the bottle). Thus the exemption from scheduling was limited to solid dosage forms only.
- The DAP debated the wording of the amended schedule entries, including whether to use the wording "14 dosage units" instead of "7 days supply".
- The amended schedule entries agreed upon by DAP were:

Schedule 2

RANITIDINE in preparations supplied in the manufacturer's original pack containing not more than 14 days supply **except** when supplied as divided preparations for oral use containing 150mg or less of ranitidine per dosage unit in the manufacturer's original pack containing not more than 7 days supply.

Schedule 4

RANITIDINE **except**:

(a) when included in Schedule 2; or

(b) in preparations supplied in the manufacturer's original pack in divided preparations for oral use containing 150mg or less of ranitidine per dosage unit containing not more than 7 days supply.

XXXXX provided a post-Meeting submission relating to Decision 2007/49-22, in which XXXXX requested that a maximum daily dose be applied to the exemption from scheduling. XXXXX originally provided a pre-Meeting comment for the February 2007 NDPSC Meeting in which XXXXX were opposed to the exemption from scheduling of ranitidine. XXXXX main points were:

- XXXXX tablets are currently available in Australia and New Zealand, however it was not clear from the current schedule wording that the maximum daily dose should not exceed 300mg.
- There was confusion around the meaning of the current Schedule 2 statement "not more than 14 days supply". Pack sizes of up to 28 tablets (150mg) were currently marketed as Schedule 2 however, at a dose of 150mg, not 300mg, per day this equates to a 28 day, not 14 day supply. XXXXX noted that this confusion would still exist with the proposed Schedule 2 entry. The Committee again noted that the setting of maximum daily doses is a matter for the regulatory authority, not the NDPSC and all the current schedule entries for H2 antagonists use the statement 'days supply'. This was first included in the schedule entries at the November 1993 DPSSC Meeting as the Committee felt that limiting the period of OTC supply was a sufficient means of restricting use of the product to OTC type indications rather than including indications in the schedule entry. This statement refers to 'days supply' at the maximum dose as per the PI.
- The Committee agreed to amend the scheduling of ranitidine when sold in solid dosage forms in manufacturer's original pack containing not more than 7 days supply with a maximum dose of 300mg per day from Schedule 2 to exempt from scheduling however, the proposed amendment does not include a maximum daily dose. XXXXX further stated that specifying the number of days supply in a pack creates confusion when taken into context of the current dosage instructions of 1-2 tablets per day. The Committee recalled that it agreed to this dosage limit as part of the decision but did not include it in the schedule entry as maximum daily dose is a registration issue rather than a scheduling issue.
- XXXXX requested that the Schedule 2 entry be further considered by the Committee with regard to including a maximum daily dose and the issue surrounding specifying the number of days supply is clarified.

The Committee noted that neither cimetidine, nizatidine nor famotidine currently have maximum daily doses applied to their respective Schedule 3 and Schedule 2 entries, however these entries do mention 'days supply'. Many schedule entries mention a maximum number of dosage units per pack. In general, the setting of a maximum daily dosage is an issue for the regulator, not the NDPSC, and as such, is controlled by the regulator through systems such as PI, CMI and product labelling. The Committee agreed that setting a maximum daily dose may only become a scheduling matter when the product is being exempted from scheduling, such as aspirin or ibuprofen.

The Committee discussed the likelihood of the proposed new schedule entry causing confusion. It was agreed that changing the entry to include the wording '14 dosage units' made the intent of the schedule entry clearer.

A Member stated that the manufacturer must ensure that the labelling of the product instructs the patient as to the maximum daily dose of the substance and that this is part of

the TGA approval process. Another Member felt that including a maximum daily dose in the schedule entry was not appropriate given that dosing is a matter for the regulatory authority and noted that as soon as an application for registration of the a product containing this substance was submitted to the regulator, the sponsor would be obligated to inform consumers of the maximum daily dose allowed. Members agreed that this was the case.

DECISION 2007/50 – 10 (Variation of Decision 2007/49-22)

The Committee agreed to vary the February 2007 NDPSC decision (2007/49-22), to exempt from scheduling ranitidine when supplied as divided preparations for oral use containing 150mg or less of ranitidine per dosage unit in the manufacturer's original pack, by removing the reference to 'days supply' from the exemption and including reference to not more than 14 dosage units.

Schedule 2 – Amendment

RANITIDINE – Amend entry to read:

RANITIDINE in preparations supplied in the manufacturer's original pack containing not more than 14 days supply **except** in divided preparations for oral use containing 150mg or less of ranitidine per dosage unit in the manufacturer's original pack containing not more than 14 dosage units.

Schedule 4 – Amendment

RANITIDINE – Amend entry to read:

RANITIDINE **except**:

(a) when included in Schedule 2; or

(b) in divided preparations for oral use containing 150mg or less of ranitidine per dosage unit when supplied in the manufacturer's original pack containing not more than 14 dosage units.

10.4 ASPIRIN WHEN COMBINED WITH PARACETAMOL, CAFFEINE OR SALICYLAMIDE

PURPOSE

The Committee considered post-Meeting comments on the scheduling of aspirin combined with caffeine, paracetamol or salicylamide

BACKGROUND

At the October 2005 NDPSC Meeting, the point was raised in relation to OTC combination analgesics, that the main point of divergence between Australia and New Zealand was those containing aspirin and caffeine. The Committee was informed that imput would be sought from XXXXX on the scheduling of combination analgesics containing aspirin. The Committee agreed to consider this matter at the February 2006 NDPSC Meeting subject to the availability of XXXXX advice. The February 2006 NDPSC Meeting agreed to defer consideration of the scheduling of aspirin as the advice from XXXXX had not yet been received.

At the February 2007 NDPSC Meeting, the Committee considered the scheduling of aspirin compound analgesics containing paracetamol, caffeine or salicylamide. After consideration of all submissions the Committee agreed that, due to the risk of nephrotoxicity, the current prescription only scheduling of aspirin when in combination with paracetamol, caffeine or salicylamide remained appropriate. The Committee also agreed to foreshadow the consideration of paracetamol when in combination only with caffeine for the June 2007 NDPSC Meeting as this was an ongoing harmonisation issue which needed to be resolved.

DISCUSSION

XXXXX provided a post-Meeting comment in which XXXXX asked for the Record of Reasons from the February 2007 Meeting be amended to reflect the fact that XXXXX had requested that Australia harmonise the scheduling of caffeine and paracetamol with New Zealand.

The Committee noted that it would be impractical to include submissions word for word in background papers. Many submissions received are very large and in order to keep the Minutes of the Meetings concise, these submissions are summarised. All points which are relevant to the Committee's consideration at hand are included in the papers. It was noted that, under ANZTPA, submissions will be made publicly available, therefore resolving this issue raised by XXXXX.

OUTCOME

The Committee noted the post-meeting comment by XXXXX but felt that amending the Record of Reasons was unnecessary.

11. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

11.1 SEDATING ANTIHISTAMINES – BROMPHENIRAMINE, CHLORPHENIRAMINE, DEXCHLORPHENIRAMINE, DIPHENHYDRAMINE, DOXYLAMINE, PHENIRAMINE, PROMETHAZINE, TRIMEPRAZINE AND TRIPROLIDINE.

PURPOSE

The Committee to consider the scheduling of sedating antihistamines when for use in children, including children < 2.

BACKGROUND

Most sedating antihistamines for use in children < 2 are currently Schedule 3 (brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine, promethazine and triprolidine). Only the diphenylpyraline and thenyldiamine Schedule 4 entries capture all use in children < 2. The wording of the Schedule 2 and 3 trimeprazine entries allow some solid and liquid preparations to be available to children < 2 as Schedule 3 while capturing the remainder as Schedule 4. Sedating antihistamines for use in children over 2 are not currently differentiated in scheduling from use in adults.

The October 2006 NDPSC Meeting:

- Noted MCC consideration of the issue of sedating antihistamines in day-night packs and agreed to foreshadow an amendment to the Schedule 2 entries for some sedating antihistamines which would restrict the inclusion of day-night packs by requiring that the day and night doses be in the same immediate container.
- Noted the recommendation that NDPSC harmonise with MCC's decision that sedating antihistamines should be classified as Prescription Medicines when indicated either singly or in combination for use in children < 2. The Committee agreed to foreshadow requiring all sedating antihistamines for use in children < 2 to be Schedule 4.

The February 2007 NDPSC Meeting considered the scheduling of sedating antihistamines as foreshadowed at the October 2006 NDPSC Meeting, including when in day-night packs and use in children < 2 years of age. The Committee:

<u>Day-night packs</u>

- Agreed to amend the Schedule 2 entries for some sedating antihistamines (brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine, promethazine, trimeprazine and triprolidine) to clarify the Committee's original intent by restricting the inclusion of day-night packs by

requiring that the day and night doses are in the same immediate container or immediate wrapper.

Children < 2

- Agreed to foreshadow consideration of the scheduling status of sedating antihistamines for children at the June 2007 NDPSC Meeting.

DISCUSSION

The February 2007 NDPSC Meeting sought comment from XXXXX and XXXXX on scheduling sedating antihistamines for use in children. Members noted:

XXXXX – did not wish to submit a comment at this time.

XXXXX

- Were asked to provide advice:
  - About any reports around the side effect profile of sedating antihistamines for use in all children (not just those < 2).
  - Whether there appeared to be differential degrees of evidence for different products/substances and whether any risks appeared to apply across the class, and whether there is also any differential based on age (i.e. < 2 and < 12).
- Advised that most antihistamines are present in multi-ingredient preparations and the assignment of adverse reactions to any particularly ingredient is often not possible. An ARTG search identified the following:

Approximate Number of Products Registered on ARTG*		
antihistamine	**single ingredient product**	**multi-ingredient product**
Brompheniramine	0	38
Chlorpheniramine	0	253
Dexchlorpheniramine	7	17
Diphenhydramine	5	59
Diphenylpyraline	0	6
Doxylamine	3	83
Pheniramine	4	29
Promethazine	16	51
Thenyldiamine	0	0
Triprolidine	0	28

*both current and cancelled entries were included because adverse reaction reporting dates back to a time when the cancelled products were marketed.

- Each antihistamine was reviewed to an extent which was considered reasonable given the large number of products for some medicines.
- *Brompheniramine* – A definitive analysis was not possible.

- *Chlorpheniramine* – A search of the entire product range was not possible but the ADRAC drug dictionary specified a number of products as being single ingredient products (probably single ingredient products when added to the ADRAC drug dictionary). 14 ADRAC reports, 1 of which describes an ADR in a child < 12. This was a serious report in that it described haemolytic anaemia and there have been isolated reports in the literature of this association.
- *Dexchlorpheniramine* – 119 ADRAC reports, of which 17 describe an ADR in children < 12 (2 additional cases of insomnia/hyperkinesia and drug ineffective were not captured by these reports). Only 2 of the reports appeared serious, one of agranulocytosis and one of coma. The case of agranulocytosis could have a number of other drug causes and the case of coma was one of breast milk transfer where the baby became unrouseable.
- *Pheniramine* – 57 ADRAC reports of which 3 describe an ADR in children < 12. Of note are reports of hallucination (2) and hepatitis. There was 1 hallucination report in an 18 year old. The hepatitis report had 3 suspected drugs including trimethoprim-sulfamethoxazole which is a more likely cause. One of the hallucination reports (9 year old) had XXXXX as the only suspected drug and a "probable" causality rating because of a positive dechallenge. The other report (4 year old) had both XXXXX and XXXXX (azatadine) as suspected drugs. Including patients of all ages, there are 5 reports of hallucinations in association with pheniramine.
- *Diphenhydramine* – 58 ADRAC reports of which 11 describe an ADR in children < 12. Of note are reports of Henoch-Schonlein purpura and a few reports of psychiatric reactions. There is one report of Henoch-Schonlein purpura in a 2 year old but the child's pre-existing conditions and use of propranolol may be more likely. The other 4 reports describe psychiatric reactions such as agitation, hallucination, and insomnia.
- *Diphenylpyraline* – 7 ADRAC reports, one of which describes an ADR in a child < 12 years (sweating and delirium in a 6 year old). The report has been assigned a "probable" causality classification because of a positive dechallenge.
- *Doxylamine* – 26 ADRAC reports of which 2 describe an ADR in a child < 12 (convulsions and cardiac disorder in 2 children who were given an overdose by their parents). The reports were derived from media reports and should be "general listed".
- *Promethazine* – 526 ADRAC reports of which 59 describe an ADR in children < 12. Of note are reports of aplastic anaemia, neutropenia, thrombocytopenia, and Stevens Johnson syndrome with a fatal outcome (in a total of 3 reports). The fatal report of Stevens Johnson syndrome in a "little child" had 3 other suspected drugs which were all a more likely cause than promethazine. The reports of neutropenia and thrombocytopenia in a 2 year old and aplastic anaemia in a 3 year old both had promethazine as the only suspected drug. There were also reports of psychiatric reactions such as agitation (8 reports), aggression (5), confusion (7), and hallucination (13). There were 84 such reports of which 21 were reported in children.
- *Thenyldiamine* – There are no products on the ARTG with this antihistamine.

- *Triprolidine* – 4 ADRAC reports involving this single ingredient product although the most recent report is 25 years old. None of these describe reports in children.
- XXXXX has received relatively few reports of adverse events of sedating antihistamines in children irrespective of age. For most medicines, there are too few reports available to base any conclusions regarding their side effect profile in children. However, pheniramine, diphenhydramine and particularly promethazine appeared to be associated with several serious psychiatric reactions, although reports of these were small in number. The greater number of reports with promethazine when compared with other antihistamines may be due to greater usage. No conclusion about differential safety profile was possible on the basis of the available ADRAC data.
- The ADRAC data suggest a possible association between sedating antihistamines and CNS adverse events in children, but the risk appeared low. The data did not indicate any clear distinction in the safety profile of sedating antihistamines with regard to child age, product type or class of ingredient; but the number of reports was too few to allow a definitive conclusion.
- A comprehensive analysis of the safety of sedating antihistamines was beyond the resources of XXXXX, but these products had been marketed for many years without any particular issues arising. While the ADRAC data should not be used as a basis for changes in scheduling, the paucity of reports on adverse events with sedating antihistamines in children should be considered reassuring.

Sedating antihistamine use in children < 2 was raised at the 36th MCC Meeting (http://www.medsafe.govt.nz/profs/class/mccMin8Feb2007.htm). Members noted:

- Some MCC members expressed a desire for further discussion about the earlier recommendation to classify these as Prescription Medicines when for children < 2. There had been a number of enquiries about the reasons for this recommendation.
- The MCC chair advised that an FDA alert had been published warning against the use of phenylephrine and pseudoephedrine in cough and cold preparations for children < 2. He added that some of the combination products implicated in the adverse reactions might also have contained antihistamines.
- It was pointed out that antihistamines were not particularly effective as cough and cold medicines while undoubtedly being misused for sedation in children < 2. The MCC Chair stated that MCC needed to consider whether or not it wanted sedating antihistamines to be used in this way, adding that there was no information to show whether the adverse reactions in children in this age group related only to promethazine or whether it was a class effect which manifested itself because promethazine was used more frequently than other sedating antihistamines. The MCC Chair concluded that it was up to the sponsor companies to prove that their products were safe and MCC had received no such information.

- It was agreed that the matter should be returned to the agenda for the 38th MCC Meeting.

Members also noted the following points from pre-meeting comments:

XXXXX

- Asserted that only phenothiazine antihistamines should be considered for stricter controls. There were several oral liquids that contain a non-phenothiazine antihistamine and decongestant for use in small children for symptomatic treatment of a head cold. Cough medicines for children are either unsafe or ineffective but combinations (e.g. phenylephrine + chlorpheniramine or brompheniramine) are useful decongestant products; they are often recommended by medical practitioners.

XXXXX

- Supported the above point.

XXXXX

- Raised concerns regarding the quality and paucity of the evidence the NDPSC had relied upon to date. [Members recalled agreement during the February 2007 consideration of this issue that more information was indeed required, hence the decision to foreshadow and to seek input from XXXXX and XXXXX].
- XXXXX noted that it appeared that the only evidence considered was the MCC data, particularly the 2001 antihistamine report. The information recorded in the Record of Reasons from this report was limited and XXXXX claimed it was important to determine the quality of scientific evidence the report offered. XXXXX requested that the report be made available for scrutiny. [Members noted that the report was referenced by MCC and appeared to have been readily obtained by other parties making pre-meeting comments].
- XXXXX questioned why this issue was foreshadowed, noting the following counter-arguments which XXXXX asserted supported no foreshadowing:
    - the long history of safe use both locally and internationally,
    - that substances should be considered individually on the basis of sound evidence and not generalised across the class; and
    - the lack of robust risk/benefit considerations.
- XXXXX asserted that the Committee had failed to adequately consider the provisions of s.52E (1) through the absence of a properly reasoned risk/benefit analysis based on evidence prior to initiating even a review of scheduling.
- XXXXX also had issue with the expansion of the consideration from children < 2 to all children. XXXXX asserted that it failed to understand the rationale for extrapolating the consideration given the apparent lack of evidence to support a review in children < 2. XXXXX asserted that it appeared that the Committee made an

assumption and was now calling for evidence to support or disprove an assumption made without any evidence before it to support that assumption.

- XXXXX asserted that it was not appropriate for the Committee to simply seek industry comment on a whim, nor ask industry to provide evidence to support status quo. XXXXX also asserted that best practice guidelines required justification for imposing any additional regulation or barriers – asserting that the onus was on the regulator to adequately demonstrate regulatory failure in the first instance, prior to investigating options to address this.
- XXXXX contended that the foreshadowed scheduling of sedating antihistamines in children, including children < 2 years of age, cannot be justified on the basis of the evidence before the Committee.
- XXXXX acknowledged the Committee's desire to address any legitimate concerns about potential abuse/hazards associated with sedating antihistamines and to investigate the matter through the public consultation process, but reiterated the need to first establish a justifiable case for any review.

XXXXX <u>February 2007 pre-meeting comment</u>

- Members recalled that XXXXX put forward two options:
  - XXXXX preferred position was to maintain the current scheduling regime for these medicines.
  - A second option was to maintain non-prescription status, but remove the label dosage instructions for children < 2, and add a statement to the effect that a pharmacist or doctor must be consulted to determine if appropriate for children < 2. [Members noted that the current ARGOM guidelines for paediatric antihistamines already require consultation with a health care professional – both for < 2 and < 12 years of age.]
- For either of these options, sponsors would be required to retain PI and CMI. All dosage instructions could be included in the PI for use of pharmacists and doctors, with the CMI providing the same information as the label, i.e. the need for a health professional to advise if suitable for a child < 2 and, if so, the appropriate dose.

XXXXX [quoted literature was not provided]

- Asserted that patients are familiar with symptoms associated with allergic conditions and the available OTC medicines used to treat them, leading to a strong pattern of self-diagnosis and self-treatment in this area.
- A review "Safety of Antihistamines in Children" (Ten Eick, 2001) concluded that different generations of antihistamines had different side effect profiles. While 1st generation antihistamines (including promethazine) were associated with sedation, cardiac disturbances and respiratory insufficiency were only seen in a small proportion of overdose cases. 2nd generation antihistamines (astemizole and terfenadine) were associated with cardiac toxicity. 3rd generation antihistamines

(such as fexofenadine) were associated with little or no sedation or cardiac toxicity. A review by The Antihistamine Impairment Roundtable concluded that the absolute risk of cardiotoxicity with older antihistamines was small (Casale, 2003).

- The pattern of side effects across classes of antihistamine was reflected by the current scheduling and availability of these classes of antihistamine; 3rd generation (Schedule 2), 1st generation (Schedule 3 or 4) and 2nd generation (largely discontinued worldwide). This appropriately reflected the risks involved in each class.
- The well-documented sedation side effect of 1st generation antihistamines was in some cases part of the effectiveness. Discomfort from failure to adequately treat symptoms associated with many allergic disorders can affect a child's quality of life. Sedating antihistamines can help provide much needed relief to these symptoms.
- The role of pharmacists in providing advice, management and monitoring was discussed. It was asserted that classification of sedating antihistamines as predominantly Schedule 3 for use in children ensured adequate access by young patients and their parents.
- A review (Love, 2006) of case reports of toddlers exposed to low doses of phenothiazines found no well-documented cases of serious morbidity or mortality resulting from isolated exposure to small doses. Considering the extensive pediatric clinical experience, widespread availability and absence of documented serious toxicity, exposure to 1-2 tablets seemed to present a minimal risk to a toddler. Greater caution may be warranted in children who are significantly < 2.
- A number of the literature reported cases of adverse events in young children taking promethazine were children given a combination of meperidine, promethazine and chlorpromazine for sedation (Nahata, 1985; Terndrup, 1989; Brown, 2001) – a combination not available in Australia.
- A letter to "Pediatrics", from 2 SIDS investigators expressed concern that links between promethazine use and SIDS continue to appear, based on flimsy evidence. They noted that half of SIDS victims have symptoms of upper respiratory tract infections at the time of their deaths and phenothiazine is in a widely used OTC cold medicine in Europe. It would be remarkable if phenothiazine were not detected in some SIDS victims, especially in Europe. Another letter argued against a change in child dosage guidelines for trimeprazine, noting that the 6 cases cited for changing the guidelines were all children with conditions which may have resulted in significant airway obstruction. XXXXX therefore asserted that experts in this field do not currently support a restriction against the use of these medicines in children over 2.
- From November 2001 to April 2006, 163 promethazine adverse events were reported to XXXXX. 10 were aged 2-12 (none were cardiovascular/breathing difficulties). During this period, there were ~1,105,778,560 days of promethazine treatment. The number of treatment days and lack of any reports of cardiovascular/breathing difficulties supports the safe use of promethazine in this age group.

- Most sedating antihistamines available in the marketplace carry appropriate statements warning against the use in children < 2.
- XXXXX believed rescheduling sedating antihistamines to Schedule 4 for use in children would not necessarily lead to a reduction in misuse. XXXXX also discussed the argument that rescheduling could lead to use of products aimed at older age groups and guessing dosing, without any involvement from a healthcare professional.
- XXXXX asserted that an Australian survey of asthmatic children found that over 65% of the children had been prescribed an antihistamine to treat their asthma, which was outside the registered indications (Donnelley, 1989). Polland and Rylance ("Inappropriate prescribing of promethazine in infants") expressed their concerns regarding the frequent prescribing of promethazine for children < 2, despite the recommendations of the manufacturer to the contrary. In a recent survey of Bahraini primary healthcare centres it was also found that 3.7% of infants (mean age 8.4 months) were prescribed promethazine, despite the fact that it was contraindicated in children < 2 (Al Khaja, 2006 "Use of promethazine in infants in primary care").
- The association of phenothiazine use and respiratory depression and apnoea in infants and young children led to the contraindication of use in children < 2 years. However, there was currently no strong evidence that would warrant the limited use of these well-tolerated and effective medicines in children < 12.
- XXXXX believed that continued availability under the supervision of pharmacists for use in older children was appropriate. Numerous sedating antihistamines have been TGA approved for child use and have been available OTC for many years. XXXXX believed that these products were safe and effective when used according to the approved indications and label directions. Restricting access to sedating antihistamines in children <12 would limit treatment options for children.
- XXXXX also noted the different salts of promethazine (particularly hydrochloride, or theoclate). Products with different promethazine salts have different approved indications in the marketplace. Promethazine theoclate is indicated for motion sickness and nausea/vomiting prevention, not sedation, and is unlikely to be used by parents as a sedating agent. XXXXX therefore presumes the theoclate salt was not under consideration for up-scheduling.

XXXXX

- It was well known from the literature that the sedative effect of phenothiazine-derivative antihistamines is far higher than the other class of antihistamines. Extrapolating phenothiazine-antihistamines effects to another class of antihistamines was not appropriate.
- Noted the AGROM guidelines only recommended stricter labelling requirements for promethazine products for use in children.
- Did not support the proposal to apply the same scheduling status to all types of antihistamines unless sufficient evidence was available against use in children.

XXXXX

- XXXXX
- XXXXX reiterated its arguments considered at the February 2007 NDPSC Meeting regarding diphenhydramine (safe and effective with no evidence of abuse or other public health issues). XXXXX therefore believed that the current scheduling for sedating antihistamines in general (and diphenhydramine in particular) remains appropriate.
- XXXXX also reiterated its review of previous NDPSC Records of Reasons, Published data and XXXXX internal records considered at the February 2007 NDPSC Meeting.
- XXXXX agreed that sedating antihistamines should only be used for children < 2 following professional consultation as was currently the case (i.e. < 2 is Schedule 3). XXXXX asserted that requiring doctor consultation would introduce unnecessary complexity, delay and cost.
- Discussed the survey mentioned by MCC which showed "an issue with antihistamine preparations being used as a sedative in young children". Details of this survey remained unclear and XXXXX asserted that it should be published. XXXXX also assert that aside from this survey, no other relevant evidence was placed before the NDPSC.
- In summary:
    - Concerns about abuse and misuse have focussed on single active sedating antihistamine products. These products are in Schedule 3.
    - The Committee has consistently agreed to maintain multi-component and day-night products as Schedule 2.
    - Combination products have been on the market for some time in Australia and New Zealand without evidence of abuse or harm from inappropriate use.
    - Diphenhydramine has a minimal risk of abuse and the multiple reports of abuse were associated with single active formulations.
    - No published evidence has been produced of abuse or misuse of diphenhydramine products in combination with other therapeutically active substances.
- XXXXX also advised that a literature search identified the following article – Nine JS et al "Fatality from diphenhydramine monointoxication: a case report and review of the infant, pediatric, and adult literature", 2006. This article concluded that diphenhydramine was a relatively non-toxic drug that was usually ingested in very large amounts when a fatality occured.

XXXXX [References not provided.]

- Did not support the proposal, asserting that the current scheduling provides an appropriate level of access to consumers while maintaining an optimal benefit/risk ratio for these products.
- XXXXX gave a description of the various classes of sedating antihistamine similar to descriptions in other comments, highlighting the variability of sedation and reiterating that concerns had only been raised with phenothiazine compounds. XXXXX also noted that cetirizine, a 2nd generation antihistamine with well documented CNS effects, was not included in the current consideration.
- XXXXX noted that according to their interpretation of RASML, paediatric preparations containing 1st generation antihistamines do not require a drowsiness sedation warning statement on the label. [Members noted that RASML statements 46, 49 and 50 read "This medication may cause drowsiness and may increase the effects of alcohol", "If affected do not drive a vehicle or operate machinery" and "If affected do not drive a motor vehicle or operate machinery". There appeared to be no paediatric specific RASML sedation warning, just generics e.g. "This product is not suitable for use in children under the age of 12 months except on professional health advice".]
- XXXXX felt that if there were concerns in relation to this class, this may be more appropriately addressed through labelling to parents/carers warning to exercise caution with the use of the product due to the potential sedative properties.
- XXXXX also discussed the ARGOM recommendations regarding paediatric products and asserted that the TGA's additional restrictions on promethazine could be construed as acknowledgement that promethazine had a more adverse safety profile which required restrictions over and above those required for other antihistamines.
- XXXXX provided comments on the data used by MCC in their antihistamines in children < 2 decision – the 2003 antihistamine report and the FDA alert warning:
    - The antihistamine report noted a possible association with promethazine and SIDS, and trimeprazine as a premedication in children and serious adverse events. XXXXX noted:
        - Both referred to use of the phenothiazine antihistamines.
        - SIDS is an active area of research yet papers quoted were over 20 years old.
        - A discussion of current guidelines on SIDS prevention failed to mention use of sedating antihistamines as a possible causative agent (Mitchell, 2007).
    - In regards to the FDA alert, it was issued following a review of all serious adverse events that were reported to the FDA. This was instigated since FDA was receiving reports of life-threatening and fatal respiratory depression in children, despite warnings on the product information document precluding use of promethazine in children < 2, and cautionary information for use in children 2 years and older.

- XXXXX noted from the February 2007 Record of Reasons the assertion that "reports of adverse events in regard to the use of promethazine, including reports of death, had only come to light in the last two years". XXXXX disagreed, asserting that promethazine had been linked with SIDS since at least 1979 and that serious adverse events with use of the more sedating 1st generation antihistamines have previously been reported in the literature.
- It was the incidence of serious and life-threatening reactions (particularly respiratory depression when used with other drugs that themselves cause respiratory depression) that lead to a reappraisal of the use of promethazine as an anaesthetic premedication by the Academy of Paediatrics in 1995.
- XXXXX also drew attention to an analysis (Cote, 2000) of adverse sedation reports in paediatric patients. In regards to sedating antihistamines concerns were only raised with promethazine. These concerns seem to indicate that a review of the scheduling of the more sedating compounds of the class was warranted. However, these safety concerns should not be extrapolated to the whole class, particularly for the less sedating compounds belonging to the alkylamine group.
- Noted that the MCC antihistamine report mentioned a survey (Dangar Research Group, 1995). SP provided some comments on this survey:
    - The questionnaire was designed to measure behavioural practices in relation to the use of paediatric medications (easily done through objective measurements) and investigating attitudes to such medications, in order to understand what drives such practices (subjective measures of attitudes could be confounded by lack of knowledge by the respondent, and/or researcher bias).
    - The results involved 130 respondents – only 26 had all children < 2. Sedating antihistamines were grouped together and included single component preparations containing 1st generation antihistamines as well as multiple-component products containing 1st generation antihistamines and a sympathomimetic agent. Practices and attitudes associated with individual products could not be differentiated.
    - In relation to use beyond the 2 recognised indications, the survey noted that a total of 16% of mothers administered sedating antihistamines when the child has difficulty sleeping. This incidence was reported for the whole category only.
    - The questionnaire allowed responders to select more than one answer. Therefore "helping the child sleep" might in fact be consequential to providing relief from the symptoms of cold, flu or allergies, and not an indicator for abuse/misuse.
- In general, and certainly for the alkylamines (chlorpheniramine, dexchlorphenlramine and brompheniramine), conditions treated by sedating antihistamines (e.g cold, flu and allergy symptoms) are self-limiting and are amenable for self treatment, with advice/counselling by a pharmacist required when used in children < 2 because of the higher risks involved with administration of these products in this age group.

- XXXXX reiterated the role of the pharmacist in providing Schedule 3 products. XXXXX also reiterated the delay and cost arguments against a Schedule 4 decision, and the argument that rescheduling could lead to use of products aimed at older age groups and guessing dosing, without any involvement from a healthcare professional.
- XXXXX provided the outcome of an ADRAC review of its affected products, and of a cumulative search of the global pharmacovigilance database for these products. This data did not reveal a tendency for inappropriate use or abuse in children.
- XXXXX noted the concern that "there is not much good quality evidence with sedating antihistamines, and that the Committee should be cautious and reschedule all members of the class" and asserted that the substantial difference between the individual members of the group meant that such an approach was inappropriate. Each substance, or at least each subclass (e.g, alkylamine, phenothiazines) should be assessed on it own merits.

XXXXX

- In the absence of more evidence of the risk and harm of these products, as a complete class, to children < 2, XXXXX does not support rescheduling to Schedule 4.
- XXXXX reiterated its arguments presented in February 2007 – lack of evidence, affect on a wide range of medicines, and that there is only evidence regarding phenothiazine antihistamines (possible sleep apnoea in infants and SIDS).
- XXXXX also advised that the use of a combination decongestant and antihistamine had been shown to be efficacious for nasal congestion and was indicated for the relief of upper respiratory mucosal congestion and hypersecretion. These were very popular product ranges. XXXXX reiterated its cost and access arguments, as well as the scenario that rescheduling could lead to use of products aimed at older age groups and guessing dosing, without any involvement from a healthcare professional (e.g. pharmacists who provide dose advice could also be professionally compromised).
- XXXXX also discussed the ARGOM noting that products for infants < 6 months containing sedating antihistamines which are not labelled for sedation must include that administration is only on the recommendation of a doctor. Supply by a pharmacist for a child < 6 months would need the pharmacist's professional judgement and the ability to justify their actions if called to account.
- XXXXX proposed that the sedating antihistamines for children < 2 be left as Schedule 3 unless there was more definitive evidence of a causal link between these products and infant mortality or morbidity. XXXXX also proposed that if such a link was identified, future consideration should be for individual medicines rather than a general class.

A number of submissions were also received from parents who use combination decongestant products (XXXXX or XXXXX). All opposed making such products available only on prescription, citing time and cost as major concerns. It was asserted

that the products were effective and provided relief for the child and parents. One commented noted that XXXXX thought some mothers used the products to sedate their babies.

Members also recalled the following from the February 2007 NDPSC Meeting:

- The case for restricting these products for children < 2 to Schedule 4 was stronger for the phenothiazine antihistamines, notably promethazine and trimeprazine. A Member asserted that there did not appear to be much evidence for the remaining sedating antihistamines. The Member noted, however, that no data did not mean "no risk", and perhaps the Committee should consider a precautionary approach to the class.
- A Member noted that it was a characteristic of most medicines, including sedating antihistamines, that there was insufficient evidence on safety (and efficacy) in this population of patients (children < 2).
- A Member noted that the FDA data included some serious flags (including deaths), although the risk from the whole class was indeterminate.
- Members noted the following provided by XXXXX:
    - A 2001 antihistamine report which touched on the subject, including:

    Promethazine

    - A 1979 study reported on a possible association with medication (including phenothiazines) and SIDS. The report noted debate about this possible association. As the literature was limited, the report was unable to resolve this debate.
    - The report noted that it was common practice in New Zealand that children < 2 were given promethazine for sedation and/or for cough in the belief that there were no known serious adverse effects. It was of concern that promethazine was easily available OTC and was also prescribed by GP's for infants without a warning. The report recommended that caution should be exercised when prescribing to infants and the datasheet should contain a warning about a possible association with SIDS.

    Trimeprazine

    - A 1985 study reported on 4 cases of an adverse cardiovascular response to oral trimeprazine as a premedication in children. Although none of the cases had a fatal outcome, all were characterised by bradycardia, hypotension and two required atropine and adrenaline infusion respectively.
    - The report noted that, as for promethazine, in New Zealand trimeprazine was given by parents to children < 2 for sedation in the belief that it had no serious adverse effects. The report asserted, however, that literature supports the possibility of adverse cardiac effects. It was recommended that trimeprazine

should be avoided in children < 2 and that the datasheet should contain a warning about potential adverse cardiac effects.

Conclusion

- There was an issue with antihistamine preparations being used as a sedative in young children. Consideration should be given to the suggestion that antihistamines that are likely to be used in children < 2 should carry warnings about the possibility of serious adverse effects. Unfortunately there was limited data in this area but the possibility that these medicines may increase the risk of SIDS in infants cannot be excluded.
- The other document considered was a FDA alert about the potential for fatal respiratory depression with promethazine in children < 2. The MCC rationale was that until there was evidence to show that other medicines in this class were not associated with this adverse event, the whole class should be treated in the same way as promethazine.

- Advice regarding the MEC guidelines, noting that the section on 'paediatric products containing antihistamines' (Chapter 9 of the current ARGOM) - states:

Paediatric products containing antihistamines

"*The dosage instructions for paediatric products containing antihistamines labelled for use in children under 2 years of age should advise (at the beginning of the directions for use in this age group) that the product is only to be given in this age group following the advice of a health care professional (see also Paediatric cold and flu products below). Where the product is indicated for sedation in children up to the age of 12 years, the label should also advise (at the beginning of the directions for use in this age group) that the product is only to be given in this age group following the advice of a health care professional.*

The labels of paediatric products containing promethazine should advise (at the beginning of the directions for use) that they should not be used in children under 12 months of age and that the advice of a doctor should be sought before administering the product to children from 12 to 24 months of age. A dose for children in the 12 to 24 month age group need not be included on the label where the product has a TGA approved published Product Information (PI) that the doctor can refer to in determining the correct dose. Where there is no PI and no dose on the label, the label must include a statement such as "Not recommended for use in children under 2 years".

In light of the above information the Committee noted a number of issues including questions of the risk/benefit of these drugs in children < 2, and whether to consider sedating antihistamines as a class or whether each substance should be considered individually. The following points were noted:

- A Member asserted that, despite there being difficulty in interpreting adverse event profiles in the Australian post-market experience, there were some significant alerts internationally about sedation and respiratory depression (with perhaps a link with SIDS, although this remains debatable). The Member argued that, on balance, it would be appropriate to take a precautionary approach and schedule all sedating antihistamines for use in < 2 as Schedule 4. A Member noted that the ADRAC reports have no denominator on exposure and therefore proper interpretation of incidence was difficult.
- A Member asserted that the evidence for the efficacy of sedating antihistamines in < 2 was pretty poor, and appeared to be largely based on extrapolation from older age groups of children. The Member asserted that < 2 was a vulnerable group of the population, that there was insufficient evidence of efficacy in this particular age group, that there was a suspicion of harm in this age group (strong for phenothiazines, but couldn't be excluded for the non-phenothiazines) and that using a sedative in this age group was not appropriate. The Member therefore recommended that the Committee employ a precautionary principle and control all sedating antihistamines for < 2 as Schedule 4 products until such time as sponsors could provide evidence that their products were not implicated, and did not behave in the same way, as the phenothiazines.
- Another Member noted that the concern was primarily with the phenothiazine sedating antihistamines where events were rare, but potentially very serious (including deaths). The Member proposed that there was a strong basis for promethazine and trimeprazine for children < 2 to become Schedule 4, but suggested that Schedule 3 may remain appropriate for the non-phenothiazines.
- A Member noted that most sedating antihistamines were already labelled not for use in children < 2 (although a few large exceptions with some popular combination sedating antihistamines).
- A Member noted that sedating antihistamines were not a homogeneous class and advocated that each should be assessed on a substance-by-substance basis. The Member also asserted that the Committee should be cautious regarding the supposed link between sedating antihistamines and SIDS, noting the lack of evidence.
- A Member again queried the efficacy of sedating antihistamines in this age group, and proposed that there seemed a possibility that the supposed efficacy was actually sedation of the child rather than an antihistamine effect. Several Members agreed that if this was the case it was an inappropriate use. Another Member noted that little was known about the pharmacokinetics of these drugs in < 2.
- A Member suggested that the regulatory authority would have addressed the efficacy question during registration. Another Member advised, however, that a substantial proportion of these products were grandfathered and entered the market with minimal evidence of efficacy.

- A Member noted some practical implications, particularly for some of the popular combination products, if parents were required to obtain a prescription. The Member reiterated that promethazine was already labelled against use < 2.

Members therefore generally agreed that there were grounds for making phenothiazine sedating antihistamines Schedule 4 for < 2, but that it was not necessarily appropriate to link the phenothiazine concern to the non-phenothiazines as a class effect.

The Committee also agreed that while the non-phenothiazines should be considered individually, there remained a paucity of information that may require application of the precautionary principle. A Member suggested, and the Committee agreed, that the individual consideration of the non-phenothiazines should be deferred to the February 2008 NDPSC Meeting to allow time for the regulator and sponsors to provide additional information, particularly data supporting the safety and efficacy in children < 2.

OUTCOME

The Committee agreed to foreshadow individual consideration of the non-phenothiazines (brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine and triprolidine) at the February 2008 NDPSC Meeting to allow additional time for the regulator and sponsors to provide further information, particularly data supporting the safety and efficacy in children < 2.

DECISION 2007/50 - 11

The Committee agreed:

- That the sedating antihistamines promethazine and trimeprazine posed a particular risk to children < 2 and as such should only be available as prescription medicines to this age group, regardless of the presence of a sympathomimetic decongestant.
- That there was currently insufficient evidence to consider that this risk applies to the remaining sedating antihistamines.
- To therefore amend the Schedule 3 entries for promethazine and trimeprazine to exclude preparations for the treatment of children under 2 years of age.

Schedule 3 - Amendments

PROMETHAZINE – Amend entry to read:

PROMETHAZINE in oral preparations **except**:

(a) when included in Schedule 2; or

(b) for the treatment of children under 2 years of age.

TRIMEPRAZINE – Amend entry to read:

TRIMEPRAZINE:

(a) in solid oral preparations **except** when include in Schedule 2; or

(b) in liquid oral preparations containing 10 mg or less of trimeprazine per mL,

except for the treatment of children under 2 years of age.

11.2 POTASSIUM CHLORIDE

PURPOSE

The Committee considered the Schedule 4 entry cut-off for potassium chloride.

BACKGROUND

The February 2006 NDPSC Meeting agreed to include oral potassium chloride (>100 mg per dosage unit) for therapeutic use in Schedule 4 on the grounds that its toxicity profile required professional oversight and to exempt oral potassium chloride preparations containing than >100 mg per dosage unit for oral rehydration therapy and for enteral feeding.

At the June 2006 NDPSC Meeting, it was brought to the Committee's attention that the February decision would inadvertently capture a large number of complementary products which contained glucosamine sulfate complexed with potassium chloride. A minute was received from XXXXX detailing the ramifications of this and providing justification as to why such complementary products should not be scheduled. The Committee agreed to vary its February decision so that only slow release preparations would be captured by the new Schedule 4 entry. The Committee also agreed to foreshadow an amendment to the Schedule 4 entry, as outlined in the February 2006 decision.

At the October 2006 Meeting the Committee considered the information provided to it regarding the toxicological profile of potassium chloride. After discussion, the Committee agreed that a 100mg cut-off was not one that was based on objective or quantitative data and was inappropriate. The Committee also agreed that the complementary medicine products containing potassium chloride complexed with glucosamine sulfate presented only a low level of risk and as such did not need to be restricted to Schedule 4. The Committee therefore decided that a 600mg cut-off would be appropriate and noted that no glucosamine sulfate complexed product currently on the ARTG would be captured.

The February 2007 NDPSC Meeting considered a post-Meeting comment regarding the 600mg cut-off for the Schedule 4 entry. A Member had noted that there were two other preparations XXXXX which contained 596 mg of potassium chloride. The 600mg cut-off would make these products unscheduled, even though with their additional potassium carbonate and bicarbonate they contained more potassium than XXXXX which, at 600mg potassium chloride, was captured by Schedule 4. Members agreed to confirm decision 2006/48-14 to include potassium chloride in Schedule 4 with a 600mg cut-off. However, the Committee also agreed to foreshadow consideration at the June 2007 NDPSC Meeting of a reduction in the cut-off for the Schedule 4 potassium chloride entry and to seek advice from XXXXX on the range of potassium chloride currently contained in glucosamine complexed products.

DISCUSSION

XXXXX advised that the highest amount of potassium chloride contained in a listed glucosamine-complexed product was 517mg.

A pre-Meeting submission was received from XXXXX stating that, at the February 2007 Meeting, the Committee concluded there was insufficient evidence to justify a cut-off change. The Committee noted that the actual wording recorded in the ratified minutes relating to this discussion was: "The Members discussed whether there was a need to vary the cut-off from 600 mg, and concluded that the Committee had insufficient evidence before it to justify a cut-off change at this time. Members therefore agreed to confirm decision 2006/48-14 to include potassium chloride in Schedule 4 with a 600mg cut-off. The Committee also agreed to foreshadow consideration at the June 2007 NDPSC Meeting of a reduction in the cut-off for the Schedule 4 potassium chloride entry". XXXXX confirmed XXXXX support for the 600mg cut-off level. XXXXX also noted that the TGA had issued a labelling directive relating to glucosamine complexed products which stated:

Contains potassium: If you have kidney disease or are taking heart or blood pressure medicines, consult your doctor or pharmacist before use. Keep out of reach of children.

XXXXX provided a pre-Meeting submission in which XXXXX recommended the potassium chloride cut-off be set at 580mg as this would capture the medicines the Committee stated concerns about at the February 2007 Meeting. XXXXX noted that reducing the cut-off to 550mg would not affect any currently listed glucosamine complexed products. However, XXXXX also stated that in the future there may be scientific evidence which supported an increase in glucosamine doses, which would lead to an increase in the amount of potassium chloride in the product. XXXXX stated that the 580mg cut-off would allow for this contingency while capturing the products the Committee was concerned about.

Members recalled that a number of submissions to the October 2006 Meeting XXXXX recommended that the Committee may wish to schedule elemental potassium rather than

potassium chloride. It was noted that this would be in keeping with the principles of Trans-Tasman harmonisation as New Zealand schedules elemental potassium rather than potassium chloride. XXXXX noted that scheduling as mmol K^+ would address issues regarding liquid and effervescent agents. [1mg K^+ is equivalent to 1.9077mg KCl. Thus 550mg KCl is equivalent to 288mg K^+. 1mmol of K^+ is equivalent to 74.6mg KCl, therefore 550mg KCl is equivalent to 7.4mmol K^+].

The Committee noted that there are a number of products included on the ARTG which contain a significant amount of potassium:-

- XXXXX contains 314.4mg K^+/ tablet (8.04mmol),
- XXXXX contains 391.0mg K^+/ tablet (10mmol),
- XXXXX contains 719.4mg K^+/ 10mL (18.4mmol),
- XXXXX contains 78.2mg K^+/ 10mL (2mmol)

Gastric lavage preparations such as XXXXX (potassium chloride) also contain large amounts of elemental potassium but these are specifically exempted from scheduling. The Committee noted that all other schedule entries for metals are listed in weight (mg/ mcg) rather than quantity (mmol).

A Member stated that they were happy with the proposed 550mg potassium chloride cut-off as this did not capture any complementary medicines but did capture the two products which contained 596mg of potassium chloride. However, they expressed concern that by scheduling only potassium chloride the Committee was missing scheduling a number of other products which had very high levels of other potassium salts which may also cause serious adverse events. The Member stated that the Committee may wish to consider the scheduling of elemental potassium and noted that New Zealand scheduled potassium in this manner.

A Member recalled that the initial issue was to do with scheduling slow-release formulations of potassium chloride, the safety concerns surrounding this substance and that this had been considered in significant detail. The Member questioned what new evidence the Committee had to reconsider the 600mg cut-off for potassium chloride and stated that all that had been brought to the Committee's attention was the fact that two products containing 596mg potassium chloride are currently exempt from scheduling.

A Member felt that the issue was the amount of elemental potassium in a product, not which salt it was and not whether the product was slow release. The Member stated that by scheduling elemental potassium all products with high levels of potassium would be captured. Another Member stated that if the Committee was to decide to schedule elemental potassium, this may inadvertently capture a large number of products that have been used safely for many years despite the amount of potassium they contained and that no safety concerns had been raised to the Committee about other potassium products. A number of Members agreed with this and noted that the original concern of the

Committee was to capture products which caused the fatality seen by the coroner, not to look at the scheduling of all potassium salts for which there was no evidence of adverse effects presented.

Members discussed the fact that cut-offs for scheduling should not be set due to the amount of a substance in a particular product, but rather that cut-offs should be set on the basis of toxicological and other relevant data.

Members discussed that the Committee's 600mg cut-off was set as per the NSW Coroner's recommendation, the consideration of XXXXX and by the fact that this would not capture any complementary products, not necessarily by any toxicological data. The Committee also noted, however that subsequent data had been obtained about the regulatory impact of this and it was determined that no other products apart from XXXXX would be captured if the cut-off was lowered to 550mg. It was also noted that both of these products were used in the same way as XXXXX and that many of the other potassium containing products were not. A Member stated that by altering the cut-off to 550mg, it would ensure the intent of the Committee's original decision. Members discussed what would be an appropriate cut-off, noting that there were no products on the ARTG containing between 550 and 596mg potassium chloride per dosage unit and agreed that 550mg was a suitable cut-off level.

DECISION 2007/50- 12

The Committee, having noted the submissions from various stakeholders, agreed to amend the Schedule 4 entry for potassium chloride so as to only capture preparations with 550mg or more per dosage unit of potassium chloride. The Committee noted this cut-off would not capture glucosamine sulfate complexed products currently on the ARTG.

Schedule 4 – Amend entry

POTASSIUM CHLORIDE in oral preparations for human therapeutic use **except**:

(a) when containing less than 550 mg of potassium chloride per dosage unit;

(b) in preparations for oral rehydration therapy;

(c) in preparations for oral use for bowel cleansing prior to diagnostic medical and surgical procedures; or

(d) in preparations for enteral feeding.

11.3 FLUORIDE

PURPOSE

The Committee considered the scheduling of fluoride for human use.

BACKGROUND

Prior to 2004 the fluorides Schedule 2 entry was:

FLUORIDES for human therapeutic use (**except** in preparations containing 15 mg/kg or 15 mg/L or less of fluoride ion):

(a) as sodium fluoride, in preparations for ingestion containing 2.2 mg or less of sodium fluoride per dosage unit; or

(b) in preparations for topical use containing 2.5 per cent or less of fluoride ion **except**:

(i) Dentrifices included in Schedule 3;

(ii) Dentrifices containing 1000 mg/kg or less of fluoride ion; or

(iii) other dental hygiene products containing 100 mg/kg or 100 mg/L or less of fluoride ion.

The 1000 mg/kg Schedule 2(b)(ii) exemption for dentrifices, and the general exemption (≤ 15 mg/kg) were introduced at the February 1986 DPSSC Meeting. Dentrifices with > 1000 mg/kg were included in Schedule 3 at the July 1987 DPSSC Meeting when it was noted that a toothpaste > 1000 mg/kg was being marketed overseas. The 2.5 % cut-off in part (b) resulted from a February 2001 NDPSC decision to harmonise with New Zealand.

The February 2004 NDPSC Meeting agreed to exempt dental hygiene products which were not dentrifices (e.g. mouth rinses) containing ≤ 220 mg/kg fluoride ion, conditional upon ≤ 120 mg/pack, CRC and label warnings against swallowing the product and use in children < six.

The June 2004 NDPSC Meeting varied the February 2004 decision by replacing “for human therapeutic use” in the fluoride entries with “for human use”. No Committee discussion was minuted regarding those non-therapeutic products for human use which were now captured (e.g. fluoride containing dental whiteners).

The October 2006 NDPSC Meeting considered the scheduling of dental whiteners or bleaches containing fluoride and agreed:

- That pastes, powders or gels containing 15 mg/kg < fluoride ion ≤ 1000 mg/kg for all applications to teeth did not warrant scheduling as there was little risk of these formulations being ingested in sufficient quantity to cause harm.
- That it was appropriate that all pastes, powders or gels for use on teeth containing > 1000 mg/kg fluoride be controlled by the Schedule 3 entry as the risks from this concentration of fluoride ion required pharmacist advice.
- That other formulations (i.e. not pastes, powders or gels) for topical oral use (220 mg/kg < fluoride ion ≤ 2.5 %) were to be Schedule 2 due to the increased risk of such formulations being ingested in a quantity which may cause harm.
- That the public health risks of topical dental hygiene, whitening or bleaching products containing 15 mg/kg < fluoride ion ≤ 220 mg/kg (unless an exempted paste, powder or gel) would be acceptably minimised through labelling, pack size limitations and a CRC requirement.

The February 2007 NDPSC Meeting considered post-meeting comment and agreed to confirm the October 2006 NDPSC decision. The Committee also noted some issues regarding cut-offs in the current fluoride entries including the Schedule 3 cut-off (particularly for non cleaning of teeth use patterns), and the possible inconsistency with the Schedule 2 cut-offs for mouth wash type products. The Members therefore agreed to foreshadow consideration at the June 2007 NDPSC Meeting of this issue.

DISCUSSION

Members recalled the following from the February 2007 NDPSC Meeting:

- It was asserted that >1000 mg/kg pastes, powders or gels for cleaning of teeth had higher chronic exposure than non cleaning products. Some Members queried this due to personal knowledge of people using non cleaning products regularly and long term.
- It was noted that the Schedule 3 cut-off to Schedule 2 was due to safety concerns about long term use of high doses of fluoride, so any cut-off change would require a revisiting of safety data. The Committee agreed that cut-off consideration should be undertaken in parallel with a revisiting of the fluoride risk assessment data.
- Members also agreed that consideration would include the possible inconsistency for mouth wash type products i.e. the Schedule 2 exemption was reduced for these products (compared to pastes etc) because of a probable increased risk, yet from 1000 mg/kg to 2.5 % these would be Schedule 2 while the same concentration range of the “less risky” pastes, powders or gels would be Schedule 3.

The February 2007 NDPSC Meeting also requested advice from XXXXX about strengths and duration of use of fluoride products. Members noted the following from XXXXX response:

- XXXXX
- There was a difficulty in finding the balance between safety and over-regulation, but felt that consistency between products should be sought as this would create greater certainty in the minds of the consumers.
- In general XXXXX was supportive of the objectives and decision in the February 2007 Record of Reasons. It generally agreed with the retention of fluoride as a scheduled substance rather than classification as therapeutic devices.
- XXXXX supported the comments from the February 2007 NDPSC Meeting relating to mouthwashes. From a clinical perspective mouthwashes containing 220mg/kg (220ppm) were advocated for daily use while higher concentrations are dentist supplied and recommended for weekly use. XXXXX believed these higher concentration mouthwashes should be scheduled.
- XXXXX agreed with the proposed cascade for pastes, powders or gels for use on teeth – exempt when ≤ 1000 mg/kg fluoride ion, Schedule 2 when 1000mg/kg < fluoride ion ≤ 2.5%, and Schedule 3 > 2.5%.
- XXXXX also believed this cascade could be applied to all products if concentrations were converted to total fluoride ion content per pack size. [A Member noted that as toothpaste was a daily use product, the fluoride exposure risk related to concentration rather than pack size. The Member noted that the original Committee concern for pastes appeared to be long term use of high doses of fluoride. Pack size could be relevant for acute exposure concerns, which in part drove the scheduling of non paste, powders or gels such as a child drinking mouth rinse. The Member asserted that the current mix of concentration and pack size restrictions may reflect both concerns.]
- XXXXX noted that XXXXX provided a comment. XXXXX strongly supported XXXXX recommendations (ii) and (iii), but gave only qualified support for recommendation (i) (profession product exemption for ≤ 5% fluoride ion).
- Recommendation (i) would certainly benefit the dental industry and the profession by removing regulatory burden and costs for a vast number of fluoride products. However, to extend the current pastes exemption (≤ 1000 mg/kg) to higher concentrations (with XXXXX suggested professional use label) would be contradictory as it would then make these products available to the public. XXXXX contends that relying on the labelling alone for high content fluoride products would not meet desirable safety requirements.

Members noted the following from XXXXX pre-meeting comment:

- The regulation of fluorides in dental products was an issue because products used exclusively in the professional practice of dentistry were not separately identified or provided for in scheduling. It was asserted that there was some misalignment in the impact of the SUSDP and the Therapeutic Goods Act and Regulations.
- The current scheduling of many dentistry products was difficult to interpret because the action of fluorides etc in the prevention of decay and the remineralisation of teeth blurs the boundary between medicines and medical devices. The Appendix A exemption for Class III medical devices adds an extra layer of complexity.
- Safeguards were in place when fluoride products are used in professional dental practice:
    - Products are used intermittently, so cumulative exposure is minimized.
    - Topical products are used in small quantities on the surfaces of teeth only.
    - The mouth is rinsed after application, and waste is not swallowed.
    - Professional use products are not supplied to the public to be taken home.
    - Fluoride in a dental restorative material (or in other material that sets hard) is not available systemically.
- The TGA Regulations set out that any therapeutic good subject to scheduling, regardless of schedule, is registrable on the ARTG. Additionally, scheduled dental hygiene products are exempted from the Excluded Goods Order, and are thus registrable. [Members noted that this was correct for oral hygiene products, but was not correct for dental bleaches or whiteners which had a separate excluded goods declaration that did not limit itself to unscheduled preparations.]
- As many of these products are not subjected to the same level of regulation in their home countries, technical files of the standard required for Australian registration were often not available and they were unable to be registered here. Therefore the Australian public is denied access to many items, routinely available overseas, and used exclusively in professional dental practice. The US has also led the way in including levels of fluoride, up to 5%, in many of these topical treatments, which is higher than those commonly found in products for public sale.
- If a technical dossier can be prepared, often the OTC evaluation costs make it uneconomical for smaller sponsors to pay for registration of these comparatively low volume products in a small and fragmented niche market in Australia.
- Continued innovation in product development and pharmaceutical delivery systems means that there will be more products which are not “pastes, powders or gels” and which are not larger volume liquid products such as mouth rinses, or washes. Existing examples are: paints, varnishes, pit & fissure sealants, mousses, foams, polishes, creams, pellets, cones, tablets, dissolving strips, etc. In addition to cleaning, whitening or bleaching, products for desensitizing also contain fluorides up to 5%.

- XXXXX therefore recommended that:

  (i) Products containing up to 5% fluoride ion, labelled "For use in the professional practice of dentistry only – Not for public supply" or words to that effect, be considered exempt from scheduling. These products should be included on the ARTG as Medical Devices.

  (ii) Fluorides in dental restorative materials, cements and polymers applied to tooth surfaces be subject to specific exemption from scheduling under Appendix A.

  (iii) Consumer products continue to be exempt goods under the current arrangements [exempt through the Excluded Goods Order, but as noted above, unless bleaches or whiteners, will not be excluded if scheduled].

- If this mechanism for professional dental use products can be introduced, there will be reduced registration costs and a dramatic increase in the number of products available for use in professional dentistry.

The Committee generally agreed that the issue regarding the difficulty of registering products on the ARTG set out above was separate to scheduling and that it would be more appropriate for sponsors with such concerns to address these to the regulator.

Members noted the following from XXXXX pre-meeting comment:

- XXXXX supported a cascade for fluorides scheduling supported by RASML. RASML did not exist when the original decision was made to capture dentifrices (> 1000 mg/kg) Schedule 3. At that time the only way to impose labelling on pastes, powders or gels for cleaning teeth (particularly in young children) was by scheduling. [Members noted that this assertion did not reflect the possible use of reverse scheduling, nor noted that if unscheduled (or scheduled whiteners or bleachers) RASML would not apply as these products would be Excluded Goods.]
- XXXXX asserted that the RASML label warnings would preclude use in children < 6 and provide a specific warning "Do not swallow" which should ameliorate the concern of the Committee over the acute toxicity of accidental ingestion of large quantities of fluoride. [Members again noted that RASML would not necessarily be mandatory.]
- With regards to the possible inconsistency with the Schedule 2 cut-offs for mouth wash type products, XXXXX asserted that this highlighted the need to consider a cascade, noting RASML's existence and considering specific additional measures that appropriately address risk whilst not imposing unnecessary control on access.
- XXXXX advised that the Australian Standards Dental Standards Group has been asked to review the most recent proposed revision to the ISO standard for dentifrices. The ISO standard had a maximum fluoride level of 1500 ppm. [Members noted that this was an overall maximum, not just a Schedule 2 maximum, and that Schedule 3 allowed such strengths (and higher) currently.]

- XXXXX also presented a commercial argument outlining trade restrictions and costs resulting from the local exclusion cut-off for toothpastes of 1000 ppm differing from other major international markets (Europe and many Asian countries - 1450 ppm; US - 1100 ppm).
- XXXXX also provided a safety review of fluoride "Safety Information for use of up to 1500 ppm Fluoride in Dentifrice". Member's noted that the detailed report was referenced, but these references were not provided. As usual for detailed pre-meeting comment, time did not allow the Secretariat to have this report independently evaluated. Members noted the following from this report:
  - Concerns with fluorosis and potential genotoxic effects have been raised with higher exposures of fluoride. However, use of a dentifrice containing up to 1500 ppm fluoride in children would be less than the acceptable daily fluoride intake of 0.045 mg/kg/day.
  - In 2005, the EU's Scientific Committee on Consumer Products (SCCP) provided an opinion on fluorine compound safety in oral hygiene products. The SCCP concluded that 1500 ppm fluoride does not pose a safety concern to children < 6.

  <u>Pharmacodynamics</u>

  - Absorbed fluoride can deposit in bone which can have beneficial results (caries resistance) or detrimental results (dental and skeletal fluorosis). Severe dental fluorosis can occur following exposure to high levels of fluoride during tooth development (usually complete by 7, so not a concern in adults). Severe skeletal fluorosis is thought to occur with ingestion of ≥ 20-80 mg/day for 10-20 years.

  <u>Pharmacokinetics</u>

  - Ingested fluoride is converted to hydrofluoric acid in the G.I. tract, from where it is readily absorbed by rapid passive diffusion. From plasma, fluoride may complex with calcified tissues and is distributed to either the intracellular or extracellular space of soft tissues or is excreted, primarily in the urine.
  - Fluoride has a high affinity for bone, but forms a reversible, sequestered pool which can be mobilized. This remobilization can occur rapidly by interstitial ionic exchange or more slowly during bone turnover. The only soft tissue which appears to have higher concentrations of fluoride than expected is the kidney, presumably since fluoride is primarily excreted via the urine.
  - A rat study showed minimal absorption of fluoride across the oral mucosa.

  <u>Toxicology</u>

  - The only proven fluoride-induced change is an increase in fluorosis due to excessive fluoride exposure in childhood. Overall, moderate dental fluorosis occurs in 1 to 2% of the population exposed to fluoride at 1 mg/L in drinking water and about 10% of population exposed to 2 mg/L; moderate to severe

fluorosis occurs in approximately 33% of population exposed to 2.4 to 4.1 mg/L in drinking water.

- There has been no correlation between increased fluoride intake due to fluoridated dental products and increased dental fluorosis. No incidence of skeletal fluorosis was found among the general U.S. population exposed to fluoridated drinking water at concentrations lower than 4 mg/L.
- Fluoride is not genotoxic except in some mammalian cell assays in vitro and often contradictory results are obtained in similar assays. The weight of evidence in animals indicates that fluoride is not a carcinogen.
- There is no evidence that exposure of pregnant females to fluoride at up to 2 mg/L in drinking water causes congenital malformations in foetuses. Likewise there are no studies linking fluoride to human reproductive effects.
- It is generally considered that the acute lethal dose of sodium fluoride in man is around 5 grams (~70 mg/kg in a 70 kg man). The acute oral LD_{50} values in male rats are 202 mg/kg in fasted rats and 471 mg/kg in fed rats; however, another study using fasted rats reported the LD_{50} values as 80-114 mg/kg of sodium fluoride. An LD_{50} of 570 mg/kg was reported for monofluorophosphate (75 mg/kg as fluoride) in rats.

Reproductive/developmental toxicity

- A review of animal and human exposure studies to fluoride shows no indication that fluoride is a teratogen. Human epidemiology studies confirm these findings.
- Studies on sodium monofluorophosphate to determine the effects on reproduction and foetal development found no fluoride-related effects on reproductive performance or embryotoxicity.

Mutagenicity

- The results of genotoxicity testing of sodium fluoride show a mix of responses. The lack of teratogenicity or embryotoxicity and the preponderance of evidence against a carcinogenic effect of fluoride lends greater weight to the absence of effective genotoxicity for sodium fluoride.

Chronic toxicity/carcinogenicity

- Detailed 3 recent chronic animal studies on sodium fluoride:
    - Study 1 (rats / mice) concluded that there were no adverse effects noted during the in-life phase except increased tooth mottling. There was equivocal evidence of carcinogenic activity in male rats with results that are interpreted as showing a marginal increase in neoplasms. There was no evidence of carcinogenicity in female rats or in male or female mice.
    - Study 2 (rats) concluded from pathology findings that fluoride affects teeth, bones, and stomach. The NOEL for this study was 1.8 mg/kg fluoride ion.

- Study 3 (dogs) concluded that there were no adverse effects on survivability, body weight or food or water consumption. The results added further evidence to show the bone-affinity of fluoride, its primary excretion in the urine, and no substantive evidence of neoplastic lesions.

- Human studies

- Epidemiology studies in humans confirm the findings of animal studies that fluoride is not linked to embryotoxicity or teratogenicity. A large number of human epidemiology studies show no link between fluoride and carcinogenicity. Therefore, the use of a 1500 ppm fluoride dentifrice should present no concern for embryo/foetal toxicity or carcinogenicity.

- The fluoridation of public water supplies has raised numerous questions about its safety, therefore, literally hundreds of studies on water fluoridation and its effects have been conducted. Of the studies aimed at determining the relationship between water fluoridation and cancer, over 50 studies have been conducted, from which it is determined there is no increased risk of cancer from drinking fluoridated water.

Safety assessment

- The fluoride exposure from a twice daily use of a dentifrice containing 1500 ppm F is presented below (calculated for a child, 1-3 years, to provide the most conservative scenario):

  Ingredient concentration = 1500 ppm (0.15%) fluoride

  Amount Used = 0.3 g

  Amount Ingested = 40%

  Frequency of Use = 2/day

  EXPOSURE = (0.0015)(0.3 g)(0.40)(1000 mg/g)(2/day) = 0.36 mg F/day

- The SCCP (2005) reported that the acceptable fluoride intake for children is up to 0.7 mg F/day. According to the SCCP and based on the fluoride exposure, if up to a 1500 ppm F toothpaste is used as recommended, there is minimal concern that children < 6 will develop fluorosis. As a result, dentifrices containing up to 1500 ppm fluoride will not pose a safety risk to consumers.

Conclusion

- Based on the available information on fluoride, a dentifrice containing up to 1500 ppm fluoride is considered safe for its intended use.

XXXXX pre-meeting comment indicated that it would welcome the opportunity to provide comment following the Committee's consideration of the XXXXX comment above.

An XXXXX fluoride risk assessment was also requested by the February 2007 NDPSC Meeting. Members were advised that no such comprehensive risk assessment was located by XXXXX. However, the following was provided:

- "Fluoride supplements in caries prevention. A literature review" prepared in 1992 for the NHMRC.
    - Reviewed the efficacy of fluoride supplements. At the time of the review it was concluded that caries incidence was low even in non-fluoridated areas, mitigating against the effectiveness of using fluoride supplements.
    - Reviewed the side effect of fluorosis, noting that fluoride supplements were an important risk factor for developing fluorosis. It was concluded that the evidence linking fluorosis to supplements was very convincing. It was also noted that while supplements cause fluorosis, other fluoride supplies, such as water and food (smaller doses spread over longer periods) did not appear to do so.
    - Fluorosis was displeasing to look at and may put at risk the undoubted benefits of water fluoridation, if the public associates fluoride with negative cosmetic effects.
    - The Review quoted the British Health Education Authority (1989) "In areas with a low prevalence of caries the general use of supplements as a public health measure is not justified except for children who are handicapped in a way which puts them more at risk to caries".
    - It was noted that the topical effect of fluoride, the principle mode by which supplements provide benefit, can be achieved by using fluoridated toothpaste.
- 1994 Toxicology report on fluoride for the DPSSC.
    - Noted that fluorosis was much more prevalent where fluoride supplements were in use. Additional (albeit marginal) fluorosis risk factors were children liking toothpaste, swallowing toothpaste and using toothpaste at an early age.
    - Questioned the use of supplements given the widespread availability of discretionary sources of fluoride (toothpaste, food and beverages). The following suggestions were made for use of daily fluoride supplements:
        - Only where living in a non-fluoridated area;
        - Should not be given before 6 months of age;
        - From 6 months to 4 yrs the dose should be 0.25 mg fluoride;
        - From 4-8yrs 0.5 mg fluoride;
        - > 8 yrs 1 mg fluoride; [the current oral sodium fluoride Schedule 2 limit]
        - Maximum dosage unit should be 0.5 mg fluoride; and
        - Should be in the form of a lozenge (to chew) rather than a tablet (to swallow).

- It was asserted that at 1000 ppm fluoride ion in toothpaste, fluoride exposure in young children prone to swallowing the paste was too high. It was recommended that 400 ppm toothpastes for use by infants be available. It was noted that the present scheduling provides for the availability of such a product.
- A view was also expressed that the 1000 ppm level in toothpastes was probably not sufficient for the control of caries in older adults and that there could be a case for the availability of toothpastes with higher fluoride. It was noted that provision for such higher fluoride toothpastes was made in the Schedule 3 entry.

- "Review of Water Fluoridation and Fluoride Intake from Discretionary Fluoride Supplements" prepared in 1999 for NHMRC.
  - Suggested the following was to reduce excessive fluoride intake:
    - Limit fluoride in infant formulae.
    - Limit fluoride supplements to those in fluoride-deficient areas not receiving fluoride in appreciable amounts from any other source, e.g. those brushing twice a day with a fluoride product would not require supplements, and supplements may not be needed where a substantial proportion of food and beverage comes from fluoridated manufacturing sites.
    - Where supplementation may be needed, limit to children > 3, with those 3-6 on 0.5 mg fluoride and those > 6 on 1 mg fluoride.
    - Avoid excessive ingestion from toothpaste and mouth rinses. Recommended that mouth rinses not to be used by children < 7. Toothpaste should be clearly labelled suitable for adult or child use, with the fluoride level, and be used under parental supervision. The label should also draw attention to the fact that overuse of the product by children < 7 may result in fluorosis.

In addition to the above papers and the schedule history in the background section, Members noted the following information from past Minutes:

<u>August 1980</u>

- Noted advice to ADEC that the use of fluoride dietary supplements in fluoridated areas should be actively discouraged.

<u>November 1980</u>

- Noted industry objection to "actively discouraged" above, on the basis that the benefits of fluoride [*supplements*] in preventing caries was well documented and adverse effects from this treatment which was widespread and used over a long period, was scanty and inconclusive.
- The Committee agreed to capture 2.2 mg dosage units of sodium fluoride for human ingestion in Schedule 2 (i.e. 1 mg fluoride ion).

<u>November 1985</u>

- Members did not support an exemption for fluoride dental rinse. The Committee considered that due to fluoridation products already available (toothpaste, tablets, drinking water), there was no need for more fluoride to be introduced. Committee noted that too much fluoride may produce fluorosis.
- It was noted that a bottle of the dental rinse contained a dose toxic to a 15 kg child.

November 1989

- Noted a letter from XXXXX which stated:
  - Oral sodium fluoride products had recommended doses exceeding those recommended by NHMRC.
  - All toothpastes should be labelled with the fluoride content.
  - Toothpastes should carry a warning statement on correct use by children.
- The Meeting agreed to refer the dosage issue to NCCTG and the toothpaste query to the Health Care Committee. An exemption request for a 0.05% sodium fluoride mouth rinse product was also referred to the Health Care Committee.

November 1990

- Noted advice that a case had not been made in support of the above mouth rinse exemption request. The Dental Health Committee expressed the view that the public already had easy access to adequate fluoride through water and toothpaste. The Committee accepted this position.

February & May 1993

- Noted a request to amend the fluoride Schedule 2 entry for supplements to not include children < 2. It was asserted that supplementary fluorides are a major risk factor in the development of fluorosis.
- Recommended that Jurisdictional Members seek advice from their Departments on a suitable age for paediatric cut-off from Schedule 4. Advice was also sought from the Child Health/Dental Health Committees.
- Members also noted public concerns concerning the lack of warning statements on fluoride containing toothpastes.

August 1993

- Members noted that Victoria had inadvertently amended its fluoride Schedule 2 entry for supplements to not include children < 2 following the May 1993 DPSSC Meeting. A great deal of negative reaction resulted e.g. pharmacists dispensing fluoride tablets in non-fluoridated areas. The Victorian Poisons Advisory Committee advised that it has since decided to again permit sale of fluoride tablets without age restriction pending DPSSC's review of fluorides.

- Noting that NHMRC was examining fluorides the Committee decided to defer consideration of this issue.

April 1994

- The Committee considered the 1994 toxicology report on fluoride (discussed above) in response to concerns over the possible occurrence of fluorosis through the unrestricted availability of fluoride supplements for small children. The Committee also noted the "Fluoride supplements in caries prevention. A literature review." discussed above.
- The Committee agreed that it would be premature to take action until the results of some additional ongoing studies were released.

August 1994

- The Committee agreed to seek advice from NHMRC on fluoride use in children, highlighting the fluorosis concerns and seeking a firm position on the use of fluoride.

November 1995

- Noted that the advice sought from NHMRC on fluorosis in children would not be forthcoming as the relevant panel no longer existed due to reorganisation of NHMRC.

November 1996

- The Committee received representations regarding fluoride use in children causing fluorosis. The Committee was also advised that toothpastes containing up to 1500 mg fluoride ion were now being sold in Europe. The Committee noted a study relating caries to fluoridated/non-fluoridated water supplies was expected to be release and agreed to defer consideration of this matter to 1997.

November 1997

- The Committee considered a paper addressing the issue of fluorosis.
- An estimated allowable daily intake of fluorides in infants was 0.07 mg/kg.
- Children who brush twice daily with fluoridated toothpaste (1000 mg/kg), were expected to absorb 0.5 mg fluoride from this source. Fluoride ingestion from water (in fluoridated areas, 1 ppm), was estimated at 2.4 mg. Taken together this gave a daily fluoride intake of 2.9 mg (daily dose rate of about 0.14 mg/kg in a 20 kg child).
- Fluorosis risk factors in a fluoridated population were fluoride in infant formulas and brushing of teeth (toothpaste ingestion). In non-fluoridated populations supplementation caused a great deal of fluorosis.
- The Committee agreed that the above supported the need to reduce the intake of fluoride by means of toothpaste ingestion in pre-school age children. It was noted that manufacturers did supply low fluoride (~400-500 mg/kg) toothpaste for children. However, the beneficial effects of fluoride in the prevention of caries in descended teeth depends on direct absorption of the fluoride into the enamel. It was asserted that

at least 1000 mg/kg fluoride in toothpaste was needed, and it was suggested that for elderly people higher levels may be required.

- The Committee agreed that scheduling did not appear to be an appropriate method of preventing fluoride exposure, given all the sources of fluoride in the Community. It was agreed that education on the effects of exposure of children was more appropriate (i.e. establishing good tooth brushing habits).

February 1998

- Advice was received from the FDA that a statement was required for all fluoride dentrifrices (gel, paste and powder) products warning: to keep out of reach of children < 6; and if accidentally swallow more than used for brushing, seek professional assistance or contact a PIC immediately. Further directions included:
    - Gel/paste (850-1150 mg/kg): Children < 2, consult a dentist or doctor. Children < 6, supervise until establish good habits minimising swallowing.
    - Gel/paste (1500 mg/kg): Children < 6, do not use unless directed by dentist or doctor. Children < 12, supervise until establish good habits minimising swallowing.
    - Powder (850 – 1150 mg/kg): Children < 6, do not use unless directed by dentist or doctor. Children < 12, supervise until establish good habits minimising swallowing.
- The Committee agreed that the main concern of the FDA appeared to be the possibility of accidental acute ingestion of toothpaste.
- The UK did not appear to require a warning statement on toothpastes.
- Consideration was deferred to gather further advice. Members confirmed that the main concern to be addressed by labelling was that of fluorosis resulting from long-term, chronic ingestion of toothpaste by children.

May 1998

- The Committee considered a number of submissions arising from the February 1998 consideration above, including several from world experts in the field of fluorosis and fluoridation. The following points were made regarding fluorosis in children:
    - Children < 2, there appeared to be no essential risk associated with fluoride exposure as did not need to use toothpaste (critical incisor dentition was not developing). Tooth brushing should still occur.
    - Children 2-6 considered at risk, and should be encouraged to use low fluoride toothpaste (400-600 mg/kg). At this strength children were unlikely to develop fluorosis in normal use, and it would provide a level of caries protection. Children 2-6 should use small amounts of toothpaste on a small brush, avoid swallowing, and spit out during and at the end of brushing.

  - Children > 6 at lower risk, fluorosis of cosmetic significance unlikely to occur.
  - Where low fluoride toothpaste was used little purpose would be served by mandating fluorosis warning statements.
- In regard to the higher strength toothpastes it was considered that parents should be encouraged to stop children swallowing toothpaste and minimise the amount of toothpaste on the toothbrush.
- The Committee agreed in light of the above that it did not wish to change the limits in the schedule entries for fluorides. Additionally, any mandated advice to prevent fluorosis (a cosmetic condition but with psychological impact) would need to ensure sufficient use to prevent caries, considered a far more serious dental condition. The Committee therefore agreed not to require mandated warning statements.

Members were advised that most Committee considerations from 1999 (prior to October 2006) concentrated on minor amendments to reflect RASML and to harmonise wording with New Zealand (i.e. replacing dentifrices). However, there were some relevant points at the following Meetings:

<u>February 2004</u>

- Noted the NHMRC "Review of Water Fluoridation and Fluoride Intake from Discretionary Fluoride Supplements" discussed above.
- The Committee considered an exemption application for a mouth rinse. The applicant asserted that the FDA had set the fluoride limit at 0.05% w/w sodium fluoride for oral rinses and that this level of fluoride had been extensively used safely in markets such as the US, UK, NZ and Australia.
- Members noted that according to the NHMRC Guideline fluoride mouth rinses should contain fluoride at a concentration of 0.05% (220 mg/kg). Members also noted that the bioavailability of fluoride from other dental hygiene products such as mouthwashes was likely to be much greater than from toothpastes.
- Members considered dental hygiene products which were not dentrifices, such as mouth washes, containing 15 mg/kg < fluoride ≤ 220 mg/kg, including possible use of mouth washes by children and the concern that this could lead to an increase in fluoride ingestion and the development of fluorosis. As the level of 220 mg/kg fluoride ion was still significantly lower than that in toothpaste the Committee considered that it was unlikely to pose any increased safety issues provided there was a limitation on the pack size (120 mg), a CRC and mandated labelling not to swallow and not recommend for use in children < 6. [Members noted that there appeared to be no consideration at this time of a possible inconsistency in that the exemption was reduced for mouth wash type products because of a probable increased risk, yet for 1000 mg/kg to 2.5 % fluoride ion these would be Schedule 2 when for the same range the 'less risky' pastes, powders or gels would be Schedule 3.]

<u>June 2004</u>

- The Committee noted that the acute toxicity level given for accidental ingestion of sodium fluoride in children was 5 mg/kg fluoride. For a 10 kg child, this equated to ingestion of ~227 mL of mouthwash containing 220 mg/L fluoride. Members remained concerned at the risk of toxicity from ingestion of more concentrated fluoride products and agreed that CRC on these products should alert consumers to the potential toxicity as well as reinforce the message that such products were not appropriate for use in young children.

October 2006

- Dental whitener product development and innovation in recent years had seen the addition of fluoride into some formulations at a level consistent with that used in cosmetic toothpastes (1000 mg/kg).
- A Member asserted that the risk of the fluoride content in teeth bleachers and whiteners would be similar to existing non-whitening dental hygiene products i.e. toothpaste, mouth rinses. The Committee agreed, noting that any separate concerns arising from the whitening active would be covered by the SUSDP entries for that active i.e. hydrogen peroxide. The Committee therefore agreed to align all fluoride containing bleaching and whitening formulations to the existing dental hygiene controls, not just pastes, powders or gels.

Members agreed that the scheduling of fluorides had evolved into a complex system as it tried to address the following:

- The risk from normal use patterns i.e. fluorosis risk from regular exposure to small quantities.
- The acute toxicity risk from accidental ingestion of a large quantity by a child.

A Member noted that some other countries allowed fewer restrictions on toothpastes with higher fluoride content. The Member also noted that while 1000 ppm was probably too strong a concentration for young children's toothpaste, it may be too low for preventing caries in the elderly.

With regard to setting specific cut-off values, the Committee welcomed the detailed data from XXXXX, but noted that this information had not been evaluated. It was agreed that both this data, and the EU review that was frequently quoted by the XXXXX report, should be evaluated, particularly noting the relevance to whether the pastes, powders and gels Schedule 2/3 cut-off should be increased.

A Member suggested that it was perhaps time to take a fresh approach to the scheduling of fluoride. The Member recommended a matrix approach, starting with using the acute toxicity of fluoride to a child to define pack size limits for a scheduling cascade, regardless of use. Another Member noted that use pattern needed to be considered in conjunction with pack sizes for evaluating the risk, particularly child access or frequency

of exposure, but did support a fresh start on the scheduling to improve the clarity of the entries.

The Committee agreed to establish a working group to look at remodelling the scheduling framework for fluoride, with an emphasis on clarity and consistency. It was agreed that the fluoride working group should be composed of XXXXX. The Committee agreed to defer consideration while the working group undertook its review, but insisted that this issue needed to be progressed in a timely manner and that the working party supply progress reports to subsequent NDPSC Meetings.

A Member suggested, and the Committee agreed, that the working parties brief could also include consideration of the proposal that professional dental products would be adequately controlled through the regulator and professional practice so as to not warrant scheduling.

OUTCOME

The Committee agreed to defer consideration of the scheduling of fluorides until such time as a fluorides working party was able to submit recommendations.

11.4 PANTOPRAZOLE

The Committee noted the inclusion of pantoprazole as a standing item on the agenda to remind the Committee that the implementation date for the June 2005 Decision, to include an entry in Schedule 3 for pantoprazole, was 1 May 2008.

11.5 PARACETAMOL AND CAFFEINE

PURPOSE

The Committee considered the scheduling of paracetamol and caffeine when combined in a compound analgesic as the only active agents.

BACKGROUND

Paracetamol is a p-aminophenol derivative that inhibits analgesic and antipyretic effects without anti-inflammatory activity. Paracetamol is currently in Schedule 4 when combined with aspirin, caffeine, or salicylamide or any derivative of these substances. It is in S2 for other therapeutic use except those unscheduled when present as the only therapeutically active substance in small quantities (in the form of either powders/sachets or tablets). Caffeine is currently an unscheduled substance, which can be included in a number of foods and beverages at concentrations of up to 320 mg/L in formulated caffeine beverages (foods, but not food additives, have a general exemption from scheduling under Appendix A).

In the 1960s – 70s in Australia, analgesic combinations containing aspirin, phenacetin (paracetamol from 1975) and caffeine, or aspirin, salicylamide and caffeine were found to be associated with a high risk of analgesic abuse and consequent analgesic nephropathy. Combinations of any two or more or paracetamol, aspirin, salicylamide, caffeine or any derivatives of these substances were rescheduled from over the counter products to prescription-only products following a recommendation from the NHMRC in 1977.

At the October 2003 NDPSC Meeting, XXXXX sought an amendment to the SUSDP to include in Schedule 2, XXXXX which contain a fixed dose of paracetamol 500 mg and caffeine 65 mg. After consideration, the Committee agreed that the current scheduling of paracetamol and caffeine remained appropriate given the inadequate evidence provided to demonstrate that the combination of caffeine and paracetamol was safe and that caffeine had potential toxic/side effects at high doses, but no convincing therapeutic benefit. Further, the Committee felt that the stimulating nature of caffeine might encourage excessive use or abuse of paracetamol.

As part of the recommendations from the Trans-Tasman Harmonisation Working Party (TTHWP), the Committee considered the scheduling of aspirin when combined with paracetamol, caffeine or salicylamide at its February 2007 Meeting. One of the submissions received in relation to this consideration was from XXXXX outlining XXXXX case for the rescheduling of paracetamol and caffeine combinations alone. The Committee noted that this combination analgesic product was currently available in New Zealand as a general sale item. The Committee discussed the exact wording of the gazette notice for the aspirin compound analgesics consideration and agreed that the wording did not capture analgesics which contained only paracetamol and caffeine. Thus, the Committee agreed that consideration of paracetamol with caffeine should be gazetted for the June 2007 Meeting.

DISCUSSION

Members recalled the following from the February 2007 NDPSC Meeting:

- XXXXX provided a large submission which discussed the scheduling of paracetamol when compounded with caffeine alone. In the submission XXXXX stated that the paracetamol/ caffeine combination analgesic had been available over the counter in many international markets (including New Zealand) for a number of years with no major adverse events or abuse of the product being reported. XXXXX particularly noted that, while a link between paracetamol and analgesic nephropathy had been suggested, phenacetin has been identified as the major risk factor and that, although paracetamol is a metabolite of phenacetin, there was no evidence that paracetamol alone would cause analgesic nephropathy. XXXXX also stated that the caffeine component acts as an analgesic adjuvant but does not increase user dependence on, or facilitate overuse of, the combination product which may, in turn, lead to an increase in adverse events.

- XXXXX also asserted that allowing a paracetamol/ caffeine combination to be supplied as a non prescription medication would meet an unmet need in the community by giving those patients who are unable to use NSAID-based analgesics due to contraindications or precautions an alternative treatment option.
- Members agreed to gazette consideration of the scheduling of paracetamol/ caffeine combinations for the June 2007 Meeting and to obtain information from both XXXXX regarding the potential for nephrotoxicity with paracetamol and caffeine only combinations.

Pre-meeting submissions

XXXXX considered the safety issues surrounding compound analgesics, particularly with relation to the potential for nephrotoxicity. XXXXX noted:

- That there are no products currently available in Australia which contain both paracetamol and caffeine alone and that there have been no adverse reports for these substances in combination.
- That habitual use of compound analgesics was thought to be due to the caffeine component of this product and, thus, agreed that the presence of caffeine in combination analgesics is undesirable and would substantially increase the risks associated with analgesics.

XXXXX provided a pre-Meeting submission in which XXXXX stated they had no objection to paracetamol in combination with caffeine being rescheduled to a Schedule 3 item. XXXXX did not explicitly recommend that it be rescheduled to a Schedule 2 item. XXXXX main points were:

- There is little published information on the long-term safety, particularly relating to the development of nephrotoxicity, of this combination. However, the results of experimental studies suggest that the potential for nephrotoxicity over the long term was low and, further, that caffeine was unlikely to enhance any nephrotoxicity from paracetamol alone.
- The caffeine component of the combination was unlikely to prove habit forming and thus its inclusion is unlikely lead to abuse or overuse of the product.
- XXXXX recommended that rescheduling to Schedule 3 is preferable to Schedule 2 as this would allow advice to be offered to consumers and ensure that the new combination was being used appropriately.

XXXXX submitted a pre-Meeting comment which stated that, given the lack of evidence to support the safety and efficacy of such a combination, it was difficult to justify the combination. XXXXX also stated concerns about the caffeine content of the product leading to potential paracetamol poisoning through excess use of the product. XXXXX provided submissions supporting this.

XXXXX provided a submission in which they recalled the principles of Trans-Tasman harmonisation and discussions at the June 2006 NDPSC Meeting about the scheduling of single active caffeine. XXXXX stated that, at the time, the Committee considered that single active caffeine did not warrant scheduling. XXXXX noted that paracetamol was currently unscheduled at a dose of 500mg/ 1000mg when compliant with other criteria. XXXXX further noted that in New Zealand the process for classification stipulates that combination products should be scheduled to the active with the most restrictive classification. Thus, if both these substances were unscheduled when compliant with certain conditions, so a combination of these substances should be when compliant with such conditions and that this is the case for this combination in New Zealand. XXXXX also noted that this combination product had been available in the UK and Ireland for many years as a general sales medicine with very few adverse events being reported. Given this and the principles of Trans-Tasman harmonisation, XXXXX requested that this combination be exempted from scheduling in Australia.

XXXXX provided a pre-Meeting comment in which XXXXX referred the Committee to XXXXX pre-Meeting submission to the February 2007 NDPSC Meeting on the matter of aspirin when combined with paracetamol, caffeine or salicylamide. Briefly this submission stated:

- In New Zealand, medicines are classified according to their active ingredients. If the medicine has more than one active ingredient, the active with the most restrictive classification determines the classification of the product. If both substances are unscheduled then the combination should also be unscheduled.
- During the last 30 years, caffeine-containing analgesics have been available globally without there being an increased association with nephropathy resulting in significant regulatory action.
- The appropriate method for determining the safety of a specific combination of substances is via the registration process conducted by the TGA, not the scheduling of the substance by the NDPSC. Any significant safety concerns would be reflected in the fact that such combinations would not be approved.

The XXXXX provided a pre-Meeting submission in which they recommend that the most appropriate schedule for paracetamol/ caffeine combinations was Schedule 3. XXXXX main points were:

- In 2006, in response to anecdotal reports of an increased demand for caffeine containing products, XXXXX conducted a community pharmacy survey on caffeine abuse from preparations currently available in Australia (this did not include paracetamol analgesics as none were available). The results showed that over 10% of pharmacists believed that requests for caffeine containing products had increased and over 20% believed that the requests were for inappropriate use.

- XXXXX stated concern about these results indicating that allowing another caffeine containing medicine on the market may lead to another avenue of inappropriate use of caffeine. XXXXX stated that the potential risk with this misuse is due to the paracetamol component of the combination leading to both liver and kidney damage.
- XXXXX suggested that, given the wide availability of caffeine and the survey results, it may be appropriate to investigate the abuse potential of caffeine before allowing the open availability of a caffeine paracetamol combination.
- Thus, XXXXX suggested that the introduction of such a combination occur as a Schedule 3 medicine as this would allow for the mandatory intervention of a pharmacist in the sale and also allow time to evaluate the safety profile and abuse potential of the product.

XXXXX provided a pre-Meeting submission in which XXXXX recommended that paracetamol/ caffeine combinations be exempted from scheduling in pack sizes up to 25 tablets and Schedule 2 medicines in larger pack sizes. The Committee noted the following points:

- Australia was unique in its scheduling of paracetamol/ caffeine combinations as Schedule 4 medicines. This scheduling had remained in place for 20 years despite the fact that there was no evidence non-phenacetin combination analgesics cause kidney disease and there had been ongoing sale of paracetamol/ caffeine combinations in overseas markets which have shown no incidence of analgesic nephropathy. XXXXX stated that in overseas markets analgesic nephropathy had decreased significantly since 1980.
- XXXXX recalled XXXXX submission to the February 2007 Meeting, particularly the safety data provided and the opinions from XXXXX "Expert Panel Meeting" held to discuss the safety and use of paracetamol/ caffeine combinations (pgs 33-35, February 2007 NDPSC Record of Reasons). XXXXX stated that overall this panel felt that the available evidence demonstrated the safety and efficacy of this combination and that thus, there was no compelling reason to not support harmonisation of scheduling between Australia and New Zealand.
- XXXXX noted the concerns expressed at the February 2007 Meeting relating to the potential for the caffeine component of combination analgesics to be habit forming. XXXXX stated that these views were not supported by the available evidence and referred again to information supplied in XXXXX February 2007 submission which stated that dependence or drug-seeking behaviour or mood-altering properties had not been observed with caffeine-containing analgesics (Fox, JM *Fundam Clin Pharmacol*. 2003 Jun, **17**(3):377-92; Bach PH *Ren Fail.* 1998 Nov, **20**(6):749-62; Feinstein AR *Clin Pharmacol Ther.* 2000 Nov, **68**(5):457-67; and Kincaid-Smith P *Med J Aust* 1969, **2**(23):1131-1135).
- XXXXX asserted that the statement in the February 2007 NDPSC Record of Reasons that there was a "lack of evidence of superiority over available analgesics" was not a

true reflection of the available literature as the literature supported the increased effectiveness and faster onset of action of paracetamol when given with caffeine across a number of pain states (Laska EM *Clin Pharmacol Ther.* 1983 Apr, **33**(4): 498-509.)

- XXXXX provided the Committee with suggested amended paracetamol Schedule 2 and 4 entries.

A PubMed search of the literature relating to efficacy of caffeine when in combination with paracetamol produced one article (Zhang WY *Drug Saf.* 2001, **24**(15): 1127-42) which found that, except in headache pain, the benefit of adding caffeine to paracetamol was equivocal. However the same search found a number of other articles (Ali Z *Curr Med Res Opin.* 2007 Apr, **23**(4):841-51; Dalaessio DJ *Headache* 1994, 34(51); and Milgardi JR *Clin Pharmacol Ther.* 1994 Nov, **56**(5):576-86) which stated that caffeine did show a significant adjuvant effect to paracetamol in a number of different pain states including tension headache and dysmenorrhoea. A comprehensive review of 33 (27 double blinded) published studies looking at caffeine as an analgesic adjuvant in a variety of pain states was undertaken by Sawynok and Yakesh (*Pharmacol. Rev.* 1993 **45**, 43-85). The review also looked at the pharmacokinetics, pharmacology, interactions and psychomotor effects of caffeine. The authors concluded that in 14 of the 27 studies there was a greater increase in pain relief with the addition of caffeine to the analgesic. It was found that this may occur at doses as low as 65mg and is most effective at the lower doses of analgesic agents and in more intense pain states. An experimental pharmacology study conducted in rodents (Engelhardt G *Arzneimittelforschung.* 1997 Aug, **47**(8):917-27) also showed that caffeine increased the antinociceptive and antipyretic effects of paracetamol, and that the increased locomotor activity caused in rodents by caffeine was diminished when caffeine was given in combination with paracetamol.

A Member observed that in XXXXX current submission, XXXXX appeared to have quoted the same studies as in their October 2003 submission to substantiate the safety and efficacy of the combination. The Member noted there was one exception to this which was an unpublished study conducted by the sponsor in 2006 in patients with dysmenorrhoea which suggested XXXXX resulted in a higher total pain relief score at 0-2 hours than paracetamol alone. The Member also reminded the Committee that at the October 2003 NDPSC Meeting, with access to the detailed submission from XXXXX and a full independent evaluation report, the Committee decided that this combination was inappropriate for inclusion in Schedule 2. Members were also reminded that the evaluation report for that submission recommended that Schedule 2 was appropriate for the combination.

A Member noted that the adverse event data supplied by XXXXX did not indicate that this combination was a cause for concern over and above any concern about paracetamol alone. However the Member stated that while the Committee had been presented with evidence to suggest that caffeine use did not lead to significant dependence problems, they still needed to be mindful of the difference between single active caffeine and

paracetamol compounded with caffeine. The Member stated that the risk from excessive paracetamol intake if someone was to take extra of a compounded preparation to increase their caffeine intake could be quite significant. The Member felt that in order to allay fears about this, experience needs to be gained with the use of the product before it could be exempted from scheduling and that a Schedule 3 listing would therefore be appropriate for this. Another Member stated that the marketing data from New Zealand indicated that there was little evidence of ongoing chronic use of the combination and that there had been no evidence provided of abuse of the combination in other markets. However, the Member noted that this issue (i.e. incidence of abuse of these fixed-dose products in other markets) had not been explored in detail in the submissions.

A Member stated that the evidence of efficacy provided to the Committee was that in approximately 50% of studies, caffeine was shown to be efficacious as an adjuvant to paracetamol. Another Member stated that there was adequate evidence of efficacy, given the combination had been approved by a number of overseas regulators. The Member reiterated the view expressed by XXXXX that if two unscheduled medicines were combined then the combination should also be unscheduled unless there was evidence that this would increase the risk to public health. Another Member noted that the Australian market had no experience with the use of combination paracetamol and caffeine products and that the argument of combining two unscheduled substances into a new unscheduled product did not necessarily work in this instance where there were concerns regarding potential caffeine habituation and also known risks of paracetamol toxicity. The Member also referred to the 2003 Guidelines for the Safe Use of Paracetamol (www.health.gov.au/internet/wcms/Publishing.nsf/Content/health-mediarel-yr2003-tw-tw03025.htm) which warned of the dangers of the misuse of paracetamol. The Member reminded the Committee that paracetamol does have risks associated with its use which may be increased by combining it with caffeine. Another Member agreed that the fact that there was no experience with a combination product in Australia was grounds for not exempting the combination product from scheduling completely. The Member felt that experience needed to be gained with the product in the Australian context before decision to exempt from scheduling could be made.

Members discussed the reasons for the October 2003 decision of the Committee not to include the combination in Schedule 2 as recommended by the evaluator. The Committee recalled that there had been inadequate evidence provided to demonstrate that the combination of caffeine and paracetamol was safe; that the Committee felt that caffeine had potential toxic effects and/or side effects at high doses, but no convincing therapeutic benefit and that the stimulating nature of caffeine might encourage excessive use or abuse of the product.

Members agreed that the reasons the Committee used to reject the October 2003 application had been mostly addressed by the evidence presented to the Committee at this Meeting, the February 2007 Meeting (for paracetamol) and at the June 2006 Meeting (for single active caffeine).

DECISION 2007/50 - 13

The Committee agreed to down schedule paracetamol when combined with caffeine from Schedule 4 as the indications for use, safety profile and potential for misuse met the criteria for a Schedule 2 medicine. The Committee was of the opinion that it would be inappropriate to consider paracetamol when combined with caffeine for exemption from scheduling until market experience had been gained with use as a Schedule 2 product.

Schedule 4 – Amendment

PARACETAMOL:

(a) when combined with aspirin or salicylamide or any derivative of these substances **except** when separately specified in these Schedules;

(b) in tablets or capsules containing more than 665 mg of paracetamol; or

(c) in individually wrapped powders or sachets of granules each containing more than 1000 mg of paracetamol.

12. PROPOSED CHANGES/ADDITIONS TO THE STANDARD FOR THE UNIFORM SCHEDULING OF DRUGS AND POISONS

12.1 SUSDP, PART 4

12.1.1 PARACETAMOL AND PHENYLEPHRINE

PURPOSE

The Committee considered the scheduling of paracetamol and phenylephrine in fixed combination.

BACKGROUND

Phenylephrine hydrochloride is a sympathomimetic amine with mainly direct effects on adrenergic receptors. It has predominantly alpha-adrenergic activity and is without significant stimulating effects on the CNS at usual doses. Its pressor activity is weaker than that of noradrenaline but of longer duration. After injection it produces peripheral vasoconstriction and increased arterial pressure; it also causes reflex bradycardia. It reduces blood flow to the skin and to the kidneys. Phenylephrine and its salts are most commonly used, either topically or by mouth, for the symptomatic relief of nasal congestion. They are frequently included in preparations intended for the relief of cough and cold symptoms. For nasal congestion, a 0.25 to 1% solution may be instilled as nasal

drops or a spray into each nostril every 4 hours as required, or phenylephrine hydrochloride may be given by mouth in doses up to 20 mg every four hours. In ophthalmology, phenylephrine hydrochloride is used as a mydriatic.

Phenylephrine was first considered by the Committee in August 1967. At that stage, all substances containing phenylephrine and its salts were put into Schedule 3. In January 1969, an exemption was made to this entry for tablets or capsules containing 0.5% or less, for other preparations for internal use containing 0.1% or less and for substances, other than preparations for internal use, containing 0.5% or less. In May 1986, ophthalmic preparations containing 5% or more were made Schedule 4. In August 1991, parenteral forms of phenylephrine were added to the Schedule 4 entry. At the November 1999 Meeting, as a result of recommendations from the trans-Tasman Harmonisation Working Party (TTHWP) which were considered at the February 1999 Meeting, the Committee amended the Schedule 2 entry for phenylephrine. It was noted at that meeting that the amendment only obtained partial harmonisation with New Zealand but the Committee decided that there should be no variation to the scheduling decision.

At the June 2004 Meeting, the Committee considered the TTHWP Decision 10/4 to remove phenylephrine from the 2-year list of unharmonised substances. At this meeting, the Committee noted that harmonisation efforts were focused on scheduling provisions and that differences in supply arrangements within both countries could lead to an unharmonised approach in respect to supply. This is the case with phenylephrine because, despite consistency with scheduling provisions, nasal preparations containing phenylephrine will continue to be sold at airports in New Zealand. The Committee decided therefore to remove phenylephrine from the 2-year list.

The October 2005 NDPSC Meeting considered the scheduling of phenylephrine with a view to harmonising with New Zealand. The November 2004 MCC considered a submission which proposed to amend the then current scheduling of phenylephrine, expressed as a percentage to accommodate liquid dose forms, to allow a cut-off point of ≤ 10 mg per oral dose form for general sale and a pharmacy-only classification for solid dose forms containing > 10 mg. The MCC recommended that phenylephrine for oral use should be a general sale medicine in products containing 50 milligrams or less per recommended daily dose and that this classification should be reviewed by a joint committee in two years. On the basis of the safety profile of oral phenylephrine and on the grounds of harmonisation with New Zealand, the October 2005 NDPSC Meeting agreed to amend the current Schedule 2 entry for phenylephrine to exempt oral preparations containing 50 mg or less per recommended daily dose. The October 2005 NDPSC meeting also agreed that the labelling issues raised by the MCC to reflect the limit on exempted use of phenylephrine for consumers under 65 years of age only should be referred to the Medicines Evaluation Committee (MEC) for consideration.

At the February 2006 NDPSC Meeting, the Committee confirmed the scheduling amendment for phenylephrine from the October 2005 Meeting.

DISCUSSION

A submission was received from XXXXX requesting rescheduling from Schedule 2 to exempt from Scheduling for paracetamol (500mg or 1000mg) and phenylephrine (10mg or 5mg) combinations. XXXXX submission asserted that:

- Both paracetamol (500mg/ 1000mg) and phenylephrine (50mg or less) were available as exempt from scheduling substances in Australia as single active agents. Both were well characterised and had commonly been used in the treatment of cold and flu symptoms. No clinical trials had been run with the combination product, however in a randomised, double blind, placebo controlled crossover trial in 16 patients, phenylephrine had been shown to be significantly more effective than placebo, producing a dose-dependent decrease in nasal airflow resistance (Cohen BM (1972), *Clinical and physiologic 'significance ' of drug-induced changes in nasal flow/resistance*. Europ J Clin Pharmacol. 5, 81-86).
- Currently there were a number of single-active unscheduled products on the market for the treatment of cold and flu symptoms; however these did not alleviate all of the major symptoms of the ailment. Access to an unscheduled combination product may be appropriate for patients in this situation and, given the economic and personal burden of the symptoms of cold and flu, it was appropriate that consumers be aware of and have ready access to a safe and effective combination for relief of cold and flu symptoms. A paracetamol /phenylephrine combination will meet this need and, given the current availability of both these substances as unscheduled, single active agents, it was not expected that allowing the combination product would cause any public health and safety concerns. Further, allowing the combination product may also provide consumers with an advantage, and increase compliance, by having them follow a simple dosage regime with a single medicine. It should also be noted that, given the recent rescheduling of pseudoephedrine containing products, there was a clear need for consumers to have access to a viable alternative treatment.
- Colds and flu are common illnesses easily recognised by consumers. They are generally self-limiting, with symptoms generally present for three to four days for colds and six to eight days for influenza. They are illnesses which are suitable for self-treatment by the consumer.
- Various paracetamol and phenylephrine combinations have been available at a general sale level internationally for many years and the combination product proposed in this submission (paracetamol 1000mg/ phenylephrine 10mg powder and paracetamol 500mg/ phenylephrine 5mg capsules) was already marketed in the UK and New Zealand and had recently been approved by the OTC Medicines section of the TGA (December 2006 for the powder and November 2005 for the capsules). In light of the recent restriction of consumer access to pseudoephedrine and the potential for increase in cost to legitimate consumers and the government, there was no public health imperative for maintaining the current Schedule 2 status of paracetamol/ phenylephrine combinations. Further, as the paracetamol/ phenylephrine combination

product would not generally cause major complications in accidental misuse or overdose, it fitted the profile of a suitable cold and flu medication to have on hand in the home.

- There had been no evidence of overuse, abuse, illicit use or diversion of the combination product and, further, there was no evidence that phenylephrine itself was subject to abuse or had any stimulant effects despite being a sympathomimetic decongestant. It was technically difficult to synthesise amphetamine-like substances from phenylephrine as it differs in structure from other, abusable phenylpropylamines and there were no recorded incidences of this occurring. There was no evidence of abuse potential with paracetamol, nor was it a candidate for diversion into illicit substances. When in combination with phenylephrine, it had no greater risk of overdose when compared to currently available unscheduled paracetamol products.
- The combination of these two substances in the one product did not decrease the safety or efficacy of either substance. There had been no reports of adverse reactions since the marketing of the combination product in New Zealand. During the period 1972 – 2005, ADRAC received 16 reports of adverse reactions (ADRs) to phenylephrine, the most common of these being allergic reactions, dizziness, nervousness and restlessness. In New Zealand, during the period 1965- 2006, 12 reports were received for ADRs with phenylephrine, the most common of these being the same as for the ADRAC reports. Data for phenylephrine ADRs from the UK MHRA for the period 1963 – 2003 showed 20 reports, the most common event reported being skin reactions to the substance. Being a sympathomimetic agent, phenylephrine also has the potential to increase blood pressure and cause tachycardia or reflex bradycardia. However, most adverse reactions for phenylephrine were seen at doses higher than those used for the relief of nasal congestion. Phenylephrine overdose may cause haemodynamic changes and cardiovascular collapse with associated respiratory depression. Phenylephrine may adversely interact with other sympathomimetic agents, beta-blockers, monoamine oxidase inhibitors or vasodilators. There was no interaction with paracetamol.
- Paracetamol ADRs are infrequent, with the most common reports relating to allergic type reactions, however anaphylaxis is rare. Haematological effects (such as thrombocytopenia) were also very rare. Paracetamol may cause hepatotoxicity in overdose or in patients with compromised hepatic function; however hepatotoxicity is unlikely to occur where this is not the case. The likelihood of analgesic nephropathy was also rare in patients taking paracetamol alone and at recommended OTC dosing regimes. Paracetamol overdose can cause the early symptoms of nausea, vomiting and the signs of liver damage will generally occur within three days. Paracetamol may interact with warfarin, barbiturates, monoamine oxidase inhibitors and metoclopramide. There is no interaction with phenylephrine.
- It was not expected that the use of this product would mask or compromise the medical management of a more serious condition, given that they symptoms of cold and flu were well recognised by consumers.

- Labelling of the product would clearly differentiate it from other XXXXX products and would prominently state the active ingredients so as to minimise the risk of it being taken with another analgesic. All required warning statements would be included on the packaging. Indications for use would also be clearly stated on the label as would a 1800 phone number which allows consumers to speak to a pharmacist about the product during business hours (an after hours recorded message would direct consumers to the Poisons Information Centre in case of emergency). The labelling would also specify use of the product only by adults and children over 12.
- All advertising of the product would adhere to the ASMI code of practice and the Therapeutic Goods Advertising Code. The advertising would also seek to educate the consumer about the responsible use of the product and direct them to seek professional advice if there was doubt or concern about their choice of medication.
- XXXXX stated rather than specifically exempt paracetamol and phenylephrine combinations from scheduling, the Schedule 2 entry for paracetamol should be reworded to remove the requirement for paracetamol to be the only therapeutically active substance when exempt from Schedule 2. This would bring the scheduling of paracetamol in line with New Zealand which allows for paracetamol alone or in combination with another therapeutically active substance to be unscheduled. XXXXX stated that as paracetamol 500mg/ 1000mg and phenylephrine 50mg are both currently permitted to be unscheduled medicines it was logical to have the combination of these substances also available as an unscheduled product. XXXXX further stated that amending the Schedule 2 entry for paracetamol in this way would not inadvertently down-schedule any current paracetamol-containing combination products and thus, have no regulatory impact other than permitting combinations of paracetamol and phenylephrine to be available at a general sale level.
- XXXXX suggested a Schedule 2 entry for paracetamol.

Two previous submissions had been made for this combination by XXXXX, the most recent in May 2006 for the October 2006 NDPSC Meeting. Both submissions were withdrawn before the Meetings due to a request by the company, however the evaluation report for the May 2006 submission had been completed. Given this, data from the evaluation report for the May 2006 submission was used here as well as data from the evaluation report for the current submission. The Secretariat also requested and received confirmation from XXXXX that XXXXX submission to this Meeting would not be withdrawn.

The NDPSC evaluation reports recommended that the Schedule 2 entry for paracetamol be amended to exempt from Scheduling paracetamol when combined with phenylephrine. The following points were highlighted in the reports:

- The proposed indications for use are for minor ailments and are suitable for self-diagnosis and treatment by the consumer. The efficacy and suitability of paracetamol as an analgesic/ antipyretic were well established. The efficacy of oral phenylephrine

as a nasal decongestant was questionable, and the only high quality published data (from randomized, double-blind, placebo controlled trials) indicated that it was no more efficacious than placebo in reducing nasal airway resistance or subjective symptoms scores. There were many products containing combinations of paracetamol with antihistamines and decongestants available for OTC use in this indication which suggested that such combinations have been determined to be suitable for self treatment in a setting in which advice and counselling are available. Whether or not this should be extrapolated to settings in which advice is not available was a contentious issue and a matter for the Committee.

- Combination products containing paracetamol and phenylephrine are available in many countries in Europe, the UK, the USA, Canada, Central and South America, Egypt, Asia and New Zealand. In the UK and New Zealand the paracetamol/ phenylephrine combination was available as a general sales product.
- Both paracetamol and phenylephrine have low potential for abuse or illicit diversion. While phenylephrine is a sympathomimetic decongestant (and has potential for similar adverse events as other sympathomimetic agents) the sponsor claimed that, due to the structural differences between it and pseudoephedrine, there is a lack of evidence of abuse or illicit use of the substance and that it is virtually impossible to synthesise amphetamine type substances from it. Paracetamol does have a high potential for harm from overdosing with the substance, but this is the same in the combination as for single component paracetamol products. Given the pack sizes (16 x 500mg for the tablets and 12 x 1000mg for the sachets) there was potential for serious hepatotoxicity if an entire pack was ingested at once, but, again, this was no greater potential that for other, unscheduled paracetamol preparations. Overdose of phenylephrine had the potential to cause hypertension and tachyarrhythmias. If the entire contents of the pack were ingested it is likely that these effects would occur.
- The New Zealand CARM database reported 12 cases of reactions to phenylephrine between 1965 and 2005, with only two events occurring more than once (conjunctivitis after local instillation of phenylephrine as eye drops and skin rash following oral use). Only two of these cases occurred after 1995. The UK MHRA database included a total of 28 reactions for combination products containing phenylephrine over the period 1963-2003, the most common of these being skin reactions and CNS disorders. The ADRAC database included 36 reports of ADRs with phenylephrine from 1972 – 2005, the majority being application site, CNS or cardiovascular reactions.
- Paracetamol is not subject to major interactions with other medications or food. Phenylephrine interacts with a number of antidepressants and may also interact with antihypertensive agents, including alpha-adrenoreceptor antagonists. It may also exhibit additive effects if used with other sympathomimetic agents. It was noted that the proposed labelling did not include any information about these interactions.
- Paracetamol has a moderately narrow therapeutic index, effective dose being 1g and serious hepatotoxicity occurring at 12g but in the non-overdose situation the risk of

toxicity is small. Phenylephrine has been used in doses of up to 250mg and given the proposed daily dose with this combination is no more than 40mg, this represents a wide therapeutic index.

- Even though the symptoms of cold and flu may occur in a number of more serious illnesses, continuing or worsening of these symptoms is likely to lead consumers to seek further medical advice. Thus, it is unlikely that the use of the paracetamol/ phenylephrine combination would mask a serious disease. There is a small risk that use of the combination may compromise the medical management of hypertension if large doses of phenylephrine are consumed over a long period, however, given the indications for use of the combination, this was unlikely.
- The proposed labelling of the product prominently lists the active ingredients, provides a telephone number for the Poisons Information Centre and the indications for use. It was felt that this would help to reduce the risk of the product being combined with other analgesic agents.
- The public health arguments for unscheduled availability, as opposed to Schedule 2, were not strongly made and consisted largely of the increased choice for consumers by having a decongestant containing product available for general sales. It was also of concern that phenylephrine in an oral dose of 10mg had not been demonstrated to be efficacious for the proposed purpose (an issue for the TGA rather than the NDPSC). However, given the absence of strong arguments against de-scheduling, in particular on safety grounds, the extensive international experience, particularly in the UK, and the issue of trans-Tasman harmonization, it was recommended that the requested amendment to the scheduling of paracetamol be made.

No pre-Meeting response to the evaluators report was received from XXXXX.

Thirty-seven (4 of which were received after the cut-off date) form letters from pharmacists were received objecting to the proposed rescheduling of the paracetamol/ phenylephrine combination. Members particularly noted the following from these form letters:

- Due to its side effects and potential drug interactions, supply of phenylephrine required professional intervention. Removal of such requirements was inconsistent with the key principles and obligations of pharmaceutical supply.
- The letters made mention of a number of different patient groups who may suffer adversely from the use of phenylephrine without counselling being provided and it was stated that these special groups would be exposed to increased risk due to this.
- It was stated that the rest of the Australian public will also be exposed to a greater risk of side effects of the medicine such as paracetamol overdose.

XXXXX provided a submission stating that XXXXX had reservations about such a large dose (1000 mg) of paracetamol being exempt from scheduling and, given the lack of efficacy of phenylephrine at the 10mg dose, patients may be tempted to take extra doses

which may lead to paracetamol toxicity. The Committee noted that this dose of paracetamol is already exempt from scheduling as a single active ingredient in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol. Therefore XXXXX stated that Schedule 2 was the appropriate schedule for this formulation unless a pack size limitation was imposed. XXXXX provided submissions supporting this.

XXXXX provided a submission in which XXXXX recalled the agreed principles of Trans-Tasman harmonisation, especially the point regarding harmonising to the least restrictive schedule. XXXXX noted that both substances were currently unscheduled in Australia when they contain less than 500/ 1000mg for paracetamol and less than 50mg phenylephrine when they are compliant with other criteria. XXXXX also noted that in New Zealand the process for classification stipulates that combination products should be scheduled to the active with the most restrictive classification. Thus, if both these substances were unscheduled when compliant with certain conditions, so a combination of these substances should be when compliant with such conditions and that this is the case for this combination in New Zealand. Thus, XXXXX requested that this combination be exempt from scheduling in Australia.

The XXXXX provided a pre-Meeting submission in which XXXXX opposed the exempting from scheduling of paracetamol and phenylephrine combination products. XXXXX main points were:

- Allowing this exemption from scheduling would set a precedent in the scheduling of fixed combination products and was not in the public interest.
- There were a large number of OTC products containing paracetamol alone or in combination and there were also a large number of OTC phenylephrine products. When complying with certain restrictions both of these substances are exempt from scheduling. This means that consumers have many sources through which they may obtain and consume paracetamol.
- The risks of hepatotoxicity from excessive paracetamol use are well recognised by pharmacists but not consumers and the potential for adverse reactions through unintentional misuse was high. Consumers may not be aware of the amount of paracetamol they were ingesting if they were taking multiple medicines and in these circumstances it was critical they have access to advice and information from professionally trained staff.

XXXXX provided a pre-Meeting submission in which XXXXX stated the current scheduling of paracetamol/ phenylephrine combinations remains appropriate. The Committee noted the following points:

- XXXXX recalled the discussion about the issues surrounding the risk of paracetamol overdose which the Committee undertook at its February 2007 Meeting. XXXXX stated that the sale of paracetamol/ phenylephrine combination products without

access to professional advice may lead to the risk of paracetamol overdose, especially if patients were unwittingly combining products which contain paracetamol. XXXXX also stated that merely relying on the dosage information on a packet is insufficient in this case.

- The efficacy of 10mg phenylephrine as a nasal decongestant was not clear and was under investigation. A possible explanation for this lack of efficacy was the poor bioavailability of the substance (38% - Meta-analysis suggests oral phenylephrine may be ineffective for nasal congestion as measured by nasal airway resistance (http://www.formularyjournal.com/formulary/article/articleDetail.jsp?id=411473)) and it may be the case that to achieve efficacy doses of up to 25mg were required. XXXXX also noted that phenylephrine has a half-life of approximately 2.5 hours (Kanfer I, Dowse R, Vuma V; *pharmacokinetics of oral decongestants*, 1993, PMID:7507589).
- XXXXX stated that, as patients would primarily be taking these combinations products for relief of nasal congestion, they may increase the dose if they were not getting any effect by either increasing the number of tablets they take, or by taking them more often. This could lead to the patient inadvertently overdosing on paracetamol and incurring the risk of liver or kidney damage or death.
- There was also the potential for interaction of this combination with other drugs including alcohol, barbiturates, beta-blockers, tricyclic antidepressants and other sympathomimetic agents.
- Thus, XXXXX believed that such combination products must be provided by trained staff who can provide advice and caution about paracetamol products and who can refer patients to pharmacists if there were any concerns raised by the patient. XXXXX also believed that any combination product which contains more than 500mg paracetamol per dosage form should be restricted to Schedule 3.

There had been discussion on XXXXX regarding the potential exemption from scheduling of paracetamol/ phenylephrine combination products. One XXXXX in particular discussed the evidence surrounding the effect of phenylephrine on blood pressure in both normotensive and hypertensive patients, citing two studies which showed that there was no effect in either of these patient groups unless a large dose (5 times the standard therapeutic) was given. XXXXX also noted that Stockley's "*Drug Interactions*" 1999 stated that there was no interaction between phenylephrine and beta-blockers, however it was noted that there was an interaction between phenylephrine and monoamine oxidase inhibitors. It was then stated that this itself did not mean that phenylephrine should be available as an exempt from scheduling substance as there were other concomitant conditions or therapeutic concerns which need to be considered. An example was given of a patient wishing to purchase phenylephrine as a treatment when they may actually be displaying signs of asthma, bronchitis or pneumonia. In this case a pharmacist could advise the patient to see a doctor. It was also strongly stated that this combination was not a life-saving medication and that pharmacies were accessible for extended day and evening hours in most places around the country 7 days a week.

XXXXX stated that this combination product did not belong in an unscheduled setting and should remain a pharmacy only medicine.

The options before the Committee took into account the following:

- To simply exclude the term 'single active' would open up the possibility of combinations of paracetamol and any other unscheduled being available to consumers in non pharmacy outlets.
- To include in the paracetamol entry that the combination with phenylephrine is exempted from scheduling would achieve harmonisation with New Zealand but not open the way for further unscheduled combinations becoming available.

A Member stated that they agreed with the evaluator that there were no compelling public health or safety reasons to prevent the combination product becoming unscheduled. The Member stated that if the Committee agreed to exempt the combination from scheduling, then phenylephrine alone in combination with paracetamol should be exempted and there should be a pack size limit applied to the exemption i.e. that other substances in combination with paracetamol should not also be exempted. Another Member agreed that a pack size limit would serve to allay concerns about unintentional overdosing with the substance. A Member stated that they agreed with the New Zealand principle of scheduling that combining two unscheduled substances should lead to the combination product being also unscheduled unless there was a specific reason for this not to occur. The Member noted that there was experience in the marketplace with this as a Schedule 2 combination product. The Member also stated that they felt the term 'single active' should not be removed from the paracetamol Schedule 2 entry and that only phenylephrine in combination with paracetamol should be exempt from scheduling.

A Member noted that there seemed to be good data presented to the Committee about the lack of side effects and drug interactions with phenylephrine. The Member stated that some submissions made too strong a point of potential side effects and drug interactions. The only drug interaction of significance is with non-selective monoamine oxidase inhibitors (MAOs) and this class of drug is seldomly prescribed these days and those prescribed MAOs are made well aware of potential interactions with OTC medicines.

There was discussion around the fact that the proposed formulation, a soluble powder, might seem to consumers to not be a "medicine" as such but more of a home remedy and thus consumers might be less inclined to follow dosing instructions carefully.

This argument was countered by a Member stating that the risk of paracetamol overdose did not seem any more likely with this combination that with paracetamol alone and made the further point that if patients were not getting relief from congestion they would be likely to seek out a single active phenylephrine product. The Member also stated that the combination product also would have the ingredients clearly listed on the label.

Members discussed the possibility that the dose of phenylephrine in the proposed products was sub-therapeutic. Members noted that the product had already been evaluated by the TGA before it was approved for use in Australia and agreed that efficacy was a matter for the regulator to establish and not for the Committee. Indeed, both the TGA's OTC Medicines Section and Medsafe (along with other overseas regulators) had determined this combination to be efficacious and so this fact must be accepted by the Committee.

A number of Members agreed with this point but felt that the issue of efficacy might also be a concern for the Committee if the phenylephrine dose was indeed sub-therapeutic as this may lead to increased dosing with the product and, thus, the potential for paracetamol toxicity. This related to 52E(1)(a), the toxicity and safety of these combined substances.

A Member stated that they had heard anecdotal evidence from patients that they found phenylephrine less effective and simply increased the dose of the product they were taking to get more of an effect. Another Member stated that the regulator had a number of mechanisms in place such as advisory statements and labelling to deal with dosing issues. In all, it was agreed that efficacy was not the purview of the NDPSC, other than determining the risk/ benefit profile and the Committee was assured that dosing instructions and advisory statements would address this.

The Committee separately agreed to pass on their concerns to the Medicines Evaluation Committee regarding the efficacy of a 50mg dose of phenylephrine.

DECISION 2007/50 - 14

The Committee agreed that the safety profile of these substances was such that allowing their fixed combination to be exempt from scheduling was reasonable. Furthermore, there was sufficient Australian market experience to support this down scheduling. Thus the Committee agreed to exempt from scheduling paracetamol 500 mg solid dose forms / 1000 mg powders or granules when combined with phenylephrine.

Schedule 2 – Amendment

PARACETAMOL for therapeutic use **except**:

(a) when included in Schedule 4;

(b) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine or when combined with effervescent agents) when:

(i) enclosed in a primary pack that contains not more than 12 such powders or sachets of granules;

(ii) compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;

(iii) not labelled for the treatment of children 6 years of age or less; and

(iv) not labelled for the treatment of children under 12 years of age when combined with phenylephrine; or

(c) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent other than (other than phenylephrine or when combined with effervescent agents) when:

(i) packed in blister or strip packaging or in a container with a child-resistant closure;

(ii) in a primary pack containing not more than 25 tablets or capsules;

(iii) compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;

(iv) not labelled for the treatment of children 6 years of age or less; and

(v) not labelled for the treatment of children under 12 years of age when combined with phenylephrine.

12.1.2 LANTHANUM

PURPOSE

The Committee considered the scheduling of lanthanum.

BACKGROUND

Lanthanum carbonate is a phosphate binder used for hyperphosphataemia in patients with chronic renal failure. Lanthanum carbonate reduces serum phosphate in end-stage renal disease (ESRD) patients. It inhibits the absorption of dietary phosphate by forming highly insoluble lanthanum phosphate complexes and binds approximately 97% of the available phosphate when it is present in a two-fold molar excess to phosphate.

The February 2006 NDPSC Meeting considered the scheduling of lanthanum after ADEC recommended registration of the substance. The Committee agreed to include lanthanum

carbonate in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitates appropriate medical diagnosis and the safe use of this medicine requires patient management and monitoring by a medical professional.

XXXXX requested that the Schedule 4 entry for lanthanum be amended to limit use to therapeutic purposes. The lanthanum entry in Schedule 4 captures all potential salts, including the carbonate salt that is used for human therapeutic use with many other lanthanum salts (including the oxide, chloride, nitrate, sulphate and hydroxide) used as common laboratory reagents. Under the current Schedule 4 wording, laboratories wishing to use these salts as reagents must hold (and pay for) a poisons permit. This constraint seems somewhat unnecessary as the rationale behind the Committee's decision was to impose controls on the use and distribution of lanthanum carbonate when required for therapeutic use, not when required for laboratory use.

XXXXX suggested either rewording the Schedule 4 entry to capture human therapeutic use of the substance only or amending the Schedule 4 entry to capture only lanthanum carbonate.

DISCUSSION

The June 2007 NDPSC Meeting noted that advice had been sought from a jurisdiction regarding the State/Territory requirements for licensing of laboratories to use Schedule 4 chemicals and the impact a change, if any, would have on the current system. The jurisdictional representative advised that Schedule 4 permits were issued on a fee-for-service basis with the process being fairly labour intensive and the preference would be to confine the lanthanum Schedule 4 entry to human therapeutic use as this would reduce the regulatory and administrative burden.

The NDPSC also noted that advice had been sought from XXXXX regarding the use of lanthanum in the veterinary setting. XXXXX advised that there was potential for lanthanum carbonate to be used for the same purpose in both animals and humans, i.e. to treat hyperphosphataemia associated with chronic renal failure. XXXXX further advised that it has been used by some veterinary specialists at veterinary schools/academic hospitals. XXXXX suggested that as the term 'therapeutic' could mean different things under different circumstances, the entry be amended to read *LANTHANUM when administered to humans or animals*.

The NDPSC noted that the Part 1(1) Interpretation in the SUSDP includes the following definition:

> ***'Therapeutic use'*** *means use in or in connection with:*
>
> *(a) preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in human beings or animals;*

(b) influencing, inhibiting or modifying a physiological process in human beings or animals; or

(c) *testing the susceptibility of human beings or animals to a disease or ailment.*

The Meeting noted that there was wide-spread and long-standing use of lanthanum in laboratories. The NDPSC agreed that the only intent of the original Schedule 4 decision was to capture lanthanum for therapeutic use.

DECISION 2007/50 - 15

The Committee agreed to amend the Schedule 4 lanthanum entry to only include therapeutic use.

The Committee also agreed that New Zealand be asked to consider similar scheduling to achieve harmonisation.

Schedule 4 – Amendment

LANTHANUM for therapeutic use.

12.2 SUSDP, PART 5

Nil items.

13. MATTERS REFEFERRED BY REGISTRATION PROCESS FOR PRESCRIPTION MEDICINES

13.1 NEW SUBSTANDES (NOT SEEN BEFORE BY NDPSC)

13.1.1 DASATINIB

PURPOSE

The Committee considered the scheduling of the new medicine dasatinib.

BACKGROUND

Dasatinib is a potent inhibitor of multiple oncogenic kinases, cellular enzymes involved in the transmission of growth signals from the cell membrane to the nucleus. Dasatinib inhibits the activity of BCR-ABL, a tyrosine kinase produced by the gene translocation [t(9,22)] associated with CML**.** It also inhibits several other kinases such as c-kit, the PDGFβ receptor, the EPHA2 receptor and the SRC family of kinases.

Dasatinib has been designated as an orphan drug in Australia. Another kinase inhibitor, imatinib, is currently registered in Australia for first-line treatment of CML.

The December 2006 ADEC Meeting recommended the approval of a submission from XXXXX to register XXXXX containing the new chemical entity dasatinib 20 mg, 50 mg and 70 mg for the indications:

Treatment of adults aged 18 years and over with:

- *all phases of chronic myeloid leukaemia (CML), with resistance or intolerance to prior therapy including imatinib;*
- *philadelphia chromosome positive (Ph+ve) acute lymphoblastic leukaemia (ALL) with resistance or intolerance to prior therapy.*

XXXXX

DISCUSSION

The June 2007 NDPSC Meeting noted the Minutes of the December 2006 ADEC meeting. XXXXX:

The NDPSC also noted the Australian approved Product Information. In particular that:

- carcinogencity studies were not performed with dasatinib;
- no specific studies had been conducted in animals to evaluate the effects of dasatinib on fertility;
- dasatinib is classified as Pregnancy Category D and may cause foetal harm when administered to a pregnant woman. Serious embryo foetal toxicity was observed in both pregnant rats and rabbits in non-clinical studies at exposure levels that were readily achievable in humans receiving therapeutic doses of dasatinib. Malformations and foetal death were also observed in rats treated with dasatinib;
- sexually active male patients taking dasatinib should use adequate contraception as the potential effects of dasatinib on sperm had not been studied;
- safety and efficacy of dasatinib in patients <18 years of age had not been established.

The NDPSC recalled its policy of:

- scheduling new chemical entities if they were needed in a life-threatening situation or for a serious disease for which safer drugs could not be used or are ineffective and the benefits from use may be acceptable despite the risk;

- excluding Pregnancy Category D anti-cancer agents from Appendix D of the SUSDP, on the basis that it was inherent to the mode of action of such agents to potentially cause foetal malformations and/or irreversible damage and for this reason, the continued exclusion of anti-cancer agents from Appendix D would remain appropriate.

The NDPSC noted that dasatinib was classified as a prescription medicine in New Zealand in February 2007 and that it was referred to the NDPSC for harmonisation consideration at agenda item 16.1.

DECISION 2007/50 - 16

The Committee agreed that dasatinib be included in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitates appropriate medical diagnosis and the safe use of this medicine requires patient management and monitoring by a medical professional. The inclusion of dasatinib in Schedule 4 also achieves harmonisation with New Zealand

Schedule 4 - New entry

DASATINIB.

13.1.2 RIMONABANT

PURPOSE

The Committee considered the scheduling of the new medicine rimonabant.

BACKGROUND

Rimonabant is a cannabinoid type-1 receptor antagonist used as an adjunct to diet and exercise for the treatment of obese patients (BMI 30 kg/m^2), and also for overweight patients (BMI > 27 kg/m^2) who have associated risk factors such as type 2 diabetes mellitus or dyslipidaemia. It is given by mouth in doses of 20 mg daily before breakfast.

DISCUSSION

The June 2007 NDPSC Meeting noted the Minutes of the December 2006 ADEC Meeting. XXXXX

The NDPSC also noted that:

- rimonabant was classified as a prescription medicine in New Zealand in February 2007 and that it was referred to the NDPSC for harmonisation consideration at agenda item 16.1;

- rimonabant is approved in approximately 30 countries including the EU and Sweden with the EU website recording authorisation in June 2006 for XXXXX (rimonabant) as an adjunct to diet and exercise for the treatment of obese patients;

- the US FDA website reported that on 13 June 2007, the Endocrinologic and Metabolic Drugs Advisory Committee would meet to discuss the efficacy and safety of a new drug application from XXXXX (rimonabant) 20 milligrams tablets as an adjunct to diet and exercise for obesity management in patients with a body mass index equal to or greater than 30 kilograms (kg) per square meter, or a body mass index equal to or greater than 27 kg per square meter if accompanied by at least one cardiovascular risk factor.

  However, a Member informed the Meeting that XXXXX issued a press release on its website on 13 June 2007 that the USFDA Endocrinologic and Metabolic Drugs Advisory Committee did not recommend approval of XXXXX (rimonabant) to the US FDA for use in obese and overweight patients with associated risk factors.

The Committee recalled its policy of scheduling new substances that have no marketed products approved for use in Australia after noting that under the therapeutic goods legislation, there are a number of avenues whereby a drug can be accessed, including personal importation, the Special Access Scheme (SAS) and clinical trials.

DECISION 2007/50 - 17

The Committee agreed to include rimonabant in Schedule 4 of the SUSDP on the grounds that the condition being treated would necessitate appropriate medical diagnosis and the safe use of this medicine requires patient management and monitoring by a medical professional. The inclusion of dasatinib in Schedule 4 also achieves harmonisation with New Zealand.

Schedule 4 – New entry

RIMONABANT.

13.1.3 SITAXENTAN

PURPOSE

The Committee considered the scheduling of the new medicin sitaxentan.

BACKGROUND

Sitaxentan is an endothelin-1 receptor antagonist that is being investigated for pulmonary hypertension and heart failure.

The December 2006 ADEC Meeting recommended the approval of a submission from XXXXX to register XXXXX containing the new chemical entity sitaxentan sodium 100 mg for the indication:

> *Treatment of pulmonary arterial hypertension (PAH) in patients with WHO Functional Class III symptoms to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease and congenital heart disease.*

XXXXX

DISCUSSION

The June 2007 NDPSC Meeting noted that sitaxentan was designated as an orphan drug in Australia.

The NDPSC noted the Minutes of the December 2006 ADEC Minutes. XXXXX

The NDPSC noted the Australian approved Product Information. In particular that:

- XXXXX is contraindicated in pregnancy and carries a Pregnancy Category X classification;

- endothelin-1 receptor antagonists as a class have consistently produced teratogenic effects in animals; and

- pregnancy must be excluded before the start of treatment, treatment must not be initiated in women of childbearing potential unless they practice reliable contraception and monthly pregnancy tests during treatment are recommended, but there is no record in the PI of post-treatment with regard to pregnancy.

The NDPSC noted that XXXXX (sitaxentan) was granted EU marketing authorisation in August 2006 with the European Medicines Agency public assessment report recording that "*it is not clear whether the teratogenic effects observed represent a class effect of endothelin receptor antagonists. Thus far, bosentan is the only registered ET receptor antagonist. Available preclinical information is insufficient to compare the reproduction toxicity findings of sitaxentan with those of bosentan.*"

The NDPSC noted that bosentan, an endothelin-1 receptor antagonist, was included in Schedule 4 by the February 2003 NDPSC Meeting. It was also noted that bosentan was a Pregnancy Category X chemical, with the XXXXX Product Information containing a warning that "*women must not become pregnant for at least three months after stopping treatment with* XXXXX", and that the February 2003 NDPSC meeting also agreed to include bosentan in a new part 6 to Appendix D.

The NDPSC noted XXXXX

DECISION 2007/50 - 18

The Committee agreed to include sitaxentan in Schedule 4 and Appendix D, part 6, of the SUSDP on the grounds that the condition being treated would necessitate appropriate medical diagnosis and the safe use of this medicine requires patient management and monitoring by a medical professional.

The Committee also agreed that New Zealand be asked to consider a similar scheduling outcome to achieve harmonisation.

Schedule 4 – New entry

SITAXENTAN**.**

Appendix D, Part 6 – New entry

SITAXENTAN for human use

13.1.4 PERFLUTREN

PURPOSE

The Committee considered the scheduling of the new medicine perflutren.

BACKGROUND

Perflutren is a perfluorocarbon gas used as either albumin- or lipid-coated microspheres for echocardiography.

The December 2006 ADEC meeting recommended the approval of a submission from XXXXX to register XXXXX for injection containing the new chemical entity perflutren 1.1 mg/mL inside lipid microspheres for the indications:

For use in patients:

- *for contrast-enhanced diagnostic ultrasound imaging to improve characterisation of focal lesions of the liver and kidney*
- *with suboptimal echocardiograms to provide opacification of cardiac chambers, improvement of left ventricular endocardial border delineation and assessment of regional wall motion at both rest and stress*

XXXXX

DISCUSSION

The June 2007 NDPSC Meeting noted the Minutes of the December 2006 ADEC Minutes meeting. XXXXX:

The NDPSC also noted the Australian approved Product Information.

The NDPSC noted that a product containing perflutren microspheres was registered on the ARTG in 2000 with the ARTG record notated "*Not scheduled. Not considered by Committee*". The Secretariat has no record of perflutren microspheres being tabled for scheduling consideration by the NDPSC.

The NDPSC noted that these agents would only be used in specific patients, administered by specialist radiologists or under professional medical supervision and used in a hospital/large medical clinic setting.

The NDPSC noted that enhancing agents for use in ultrasonic and magnetic resonance imaging are included as a general exemption under Appendix A of the SUSDP.

A Member requested that perflutren be included in the SUSDP index and cross-referenced to enhancing agents.

OUTCOME

The Committee agreed that perflutren was captured by the Appendix A exemption "*enhancing agents for use in ultrasonic and magnetic resonance imaging*" on the grounds that this is consistent with the scheduling of other radiographic contrast media and that the product is supplied directly to hospital radiology departments and only administered by trained personnel.

The Committee also agreed that New Zealand be asked to consider a similar scheduling outcome to achieve harmonisation.

13.1.5 PARICALCITOL

PURPOSE

The Committee considered the scheduling of the new medicine paricalcitol

BACKGROUND

Paricalcitol is a synthetic analog of calcitriol, the metabolically active form of vitamin D indicated for the treatment of secondary hyperparathyroidism in chronic kidney disease (CKD). Its biological actions are mediated through binding of the vitamin D receptor.

This activity results in selective activation of vitamin D responsive pathways and inhibition of parathyroid hormone (PTH) synthesis and secretion.

The December 2006 ADEC Meeting recommended the approval of a submission from XXXXX to register XXXXX containing the new chemical entity paricalcitol 1 μg, 2 μg and 4 μg and XXXXX containing paricalcitol 5 μg/1 mL and 10 μg/2 mL for the indication:

> *Treatment of the biochemical manifestations of secondary hyperparathyroidism associated with chronic kidney disease.*

XXXXX

DISCUSSION

The June 2007 NDPSC Meeting noted the Minutes of the December 2006 ADEC Meeting and the Australian approved Product Information.

DECISION 2007/50 - 19

The Committee agreed that paricalcitol be included in Schedule 4 of the SUSDP on the grounds that the condition being treated would necessitate appropriate medical diagnosis and the safe use of this medicine requires patient management and monitoring by a medical professional.

The Committee also agreed that New Zealand be asked to consider a similar scheduling to achieve harmonisation.

Schedule 4 – New entry

PARICALCITOL.

13.1.6 FACTOR VIII INHIBITOR BYPASSING FRACTION

PURPOSE

The Committee considered the scheduling of the new medicine factor eight inhibitor bypassing activity (FEIBA)

BACKGROUND

FEIBA is a Prothrombin Complex Concentrate (PCC) derived from human plasma. It contains the coagulation factors, activated FVIIa, IXa and Xa as well as the proenzymes FII, FVII, FIX and FX.

The October 2006 ADEC Meeting recommended the approval of an application from XXXXX to register XXXXX containing the new biological entity Factor Eight Inhibitor Bypassing Fraction 500 IU and 1,000 IU for the indication:

> *Second line therapy for the control of spontaneous bleeding episodes and use in surgery, in haemophilia A or B patients with inhibitors, for whom recombinant human factor VIIa is unavailable or has failed.*

XXXXX

DISCUSSION

The June 2007 NDPSC Meeting noted the Minutes of the October 2006 ADEC Meeting and the Australian approved Product Information.

The NDPSC also noted that product has been supplied in Australia under the Special Access Scheme for many years and that due to the rarity of haemophilia patients with inhibitors, FEIBA has been designated as an orphan drug. Alternative treatments are Recombinant Factor VIIa XXXXX and a non-activated XXXXX which is not registered for this indication.

The NDPSC noted that FEIBA was classified as a prescription medicine in New Zealand.

The NDPSC recalled that historically it had a standing policy of not scheduling blood products given that scheduling may place unwarranted restrictions on the supply of products which already have adequate Commonwealth and State/Territory controls.

The scheduling of blood products was considered at the October 2005, February 2006 and June 2006 NDPSC Meetings with the latter Meeting agreeing:

- to put this policy on hold pending the outcome of a 12 month consultation period with the blood sector by the National Blood Authority's Jurisdictional Blood Committee (NBA JBC) on the scheduling of blood products;

- that if applications for similar products were received before the completion of the NBA JBC consultation, the Secretariat would inform the applicant directly that the product would not be considered until after the consultation period.

The NDPSC noted that FEIBA was listed for harmonisation at the June 2006 NDPSC Meeting, but was deferred pending the outcome of the NBA JBC consultation.

The Meeting was informed that the 12 month NBA JBC consultation was due to finish in October 2007 with the report expected to be available for the February 2008 NDPSC Meeting.

OUTCOME

The Committee agreed to defer scheduling consideration of factor eight inhibitor bypassing activity until completion of the National Blood Authority's Jurisdictional Blood Committee's 12 month consultation period

13.1.7 RANIBIZUMAB

PURPOSE

The Committee considered the scheduling of the new medicine ranibizumab

BACKGROUND

Ranibizumab is a recombinant humanised monoclonal antibody fragment related to bevacizumab that binds to and inhibits vascular endothelial growth factor (VEGF), a stimulant of angiogenesis that is thought to play a role in the neovascularisation and retinal changes associated with age-related macular degeneration.

The February 2007 ADEC Meeting recommended approval of an application from XXXXX to register XXXXX containing the new biological entity ranibizumab (rbe) 1.8 mg/0.3mL and 3.0 mg/0.3mL for the indication:

> *the treatment of neovascular ("wet") age-related macular degeneration (AMD).*
>
> XXXXX *0.5 mg or 0.3mg is recommended to be administered by intravitreal injection once a month.*

XXXXX

DISCUSSION

The June 2007 NDPSC Meeting noted the Minutes of the February 2007 ADEC Meeting XXXXX

The NDPSC also noted the Australian approved Product Information.

DECISION 2007/50 - 20

The Committee agreed that ranibizumab be included in Schedule 4 of the SUSDP on the grounds that the condition being treated would necessitate appropriate medical diagnosis and the safe use of this medicine requires administration and patient management and monitoring by a medical professional.

The Committee also agreed that New Zealand be asked to consider similar scheduling to achieve harmonisation.

Schedule 4 – New entry

RANIBIZUMAB.

13.1.8 PENTASTARCH

PURPOSE

The Committee considered the scheduling of the new medicine pentastarch including the possibility of a Schedule A exemption.

BACKGROUND

Pentastarch is an etherified starch. These are starches that are composed of more than 90% of amylopectin and that have been etherified to varying extents. In pentastarch an average of 4 to 5 of the hydroxy groups in each 10 D-glucopyranose units of the starch polymer have been converted to OCH2CH2OH groups. Etherified starches are plasma volume expanders used in the management of hypovolaemic shock.

The application to register pentastarch did not go through the ADEC process; rather it was handled through the Peer-Review process of the DSEB. The Peer Review Process is as follows (taken from the document *TGA - Australian Regulation of Prescription Medicine Products*):

- If a product is already marketed and the current application seeks only to extend its use, and there is agreement amongst evaluators, the senior medical officer and the company, then the advice may be sought from the Peer Review Committee. The summary is sent to the sponsoring applicant who is able to submit a response dealing with issues raised in the summary and those not previously addressed in the evaluation report. This response goes direct to the Peer Review Meeting and is not edited by the senior officer.
- The Peer Review Committee is a group of senior medical officers from all area of Prescription Medicine Regulation that meet to consider non-contentious applications for other than new medicines. All senior medical officers within DSEB and ADRAC are requested to attend peer review meetings. These include officers from other streams, experimental drugs and the adverse reactions area.
- A delegate within the TGA is the decision-maker who takes into account the advice of the Peer Review Committee in reaching a decision to approve or reject a product. Approvals may have conditions associated with them.

On 6th November 2006, the DSEB delegate approved the submission from XXXXX containing the new chemical pentastarch XXXXX for the indication:

Therapy and prophylaxis of hypovolaemia;

Currently the other plasma volume expanders dextran, polygeline and gelatin – succinylated are all unscheduled substances.

These items (along with hetastarch and pentastarch) were considered at the November 1999 TTHWP Meeting as they were Part III substances in New Zealand but unscheduled in Australia. XXXXX Members were concerned that scheduling plasma expanders as Schedule 4 would create difficulties in use for the armed forces and ambulance officers. The TTWHP considered the option of moving these substances into Schedule 2 or 4, however decided that as long as these substances continued to be evaluated by DESB and MOH, they should be exempted in the same manner as water for injections or dextrose infusions. The TTHWP advised the NDPSC to recommend to New Zealand to adopt this scheduling.

The February 2000 NDPSC Meeting endorsed the TTHWP recommendation and recommended to New Zealand that they harmonise with Australia on the scheduling of these substances. These substances are all currently general sale in New Zealand.

DISCUSSION

Comment was received from XXXXX opposing an Appendix A exemption for this substance. It was stated that medicines such as this should not be given without Schedule 4 provisions being in place. It was also stated that, in the absence of such provisions, there would not be sufficient assurance that adequate medical supervision would be carried out.

XXXXX provided a comment in which it was stated that XXXXX had no view on the matter for consideration.

Members discussed whether the Jurisdictional Blood Committee review of recombinant and fractionated blood products was relevant to the scheduling of this substance. Members agreed that as pentastarch and the other plasma volume expanders dextran, polygeline and gelatin – succinylated were not blood products, the review was not relevant in this instance. Members also noted that all other plasma volume expanders were currently unscheduled.

Members discussed that pentastarch and the other plasma volume expanders were likely to be used in emergency medicine by ambulance or emergency services officers as well as doctors. The Committee were reassured that the substances were unlikely to be used outside of these supply chains and therefore felt that an Appendix A exemption was more

appropriate as it would allow access for ambulance or emergency services officers to use the substances.

DECISION 2007/50 - 21

The Committee agreed to:

- Exempt pentastarch under Appendix A "dextrans, gelatin - succinylated & etherified starches" on the grounds that the product is supplied directly to hospital departments or trained personnel and only administered by trained personnel; and

- Recommend that New Zealand consider including pentastarch, gelatin - succinylated & etherified starches as general sale items as New Zealand do not incorporate Appendix A into their scheduling.

Appendix A – New entry

DEXTRANS, GELATIN - SUCCINYLATED & ETHERIFIED STARCHES used as plasma substitutes/ blood volume expanders.

13.1.9 GALSULFASE

PURPOSE

The Committee considered the scheduling of the new medicine galsulfase.

BACKGROUND

Galsulfase is recombinant human arylsulfatase B and is used as enzyme replacement for the treatment of mucupolysaccharidosis VI (Maroteaux-Lamy syndrome), a lysosomal storage disorder that results in the accumulation of the glycosaminoglycan substrate dermatan sulfate in the lysosomes with consequent widespread tissue and oxygen dysfunction.

MPS VI is a rare disorder characterised by the congenital absence of N-acetylgalactosamine 4-sulfatase. Galsulfase was designated as an orphan drug in Australia as there were no registered medicines for the treatment of this condition.

On 16 February 2007, the TGA Delegate granted approval to XXXXX for the registration of XXXXX, containing galsulfase concentrated solution, 5 mg in 5 mLs for the treatment of mucopolysaccharidosis type VI (MPS VI or Maroteaux-Lamy syndrome).

XXXXX was an orphan drug for which TGA was able to obtain US FDA evaluations. In these situations, it is the policy of the TGA Drug Safety and Evaluation Branch that the

product should be registered without referral to ADEC or without taking it to the Peer Review Meeting.

The TGA Delegate obtained the US FDA unedited evaluations and these were used in place of a TGA clinical evaluation.

The Product Information was approved on 19 February 2007.

DISCUSSION

The June 2007 NDPSC Meeting noted the TGA Delegate's summary. XXXXX

The NDPSC also noted the Australian approved Product Information.

DECISION 2007/50 - 22

The Committee agreed that galsulfase be included in Schedule 4 of the SUSDP on the grounds that the condition being treated would necessitate appropriate medical diagnosis and the safe use of this medicine requires administration and patient management and monitoring by a medical professional.

The Committee also agreed that New Zealand be asked to consider a similar scheduling to achieve harmonisation.

Schedule 4 – New entry

GALSULFASE.

15. MATTERS REFERRED BY THE MEDICINES EVALUATION COMMITTEE (MEC)

Nil items.

16. MATTERS REFERRED BY THE MEDICINES CLASSIFICATION COMMITTEE (MCC) OF NEW ZEALAND

16.1 MCC NEW MEDICINES

PURPOSE

The Committee considered the inclusion in Schedule 4 (S4) of new medicines classified as Prescription Medicines in New Zealand.

BACKGROUND

The XXXXX meetings, held in February 2007, agreed to classify the new medicines below, i.e. abatacept, aliskiren, darunavir, fosaprepitant, lapatinib, nepafenac, nilotinib, paliperidone, ruboxistaurin, rimexolone and vildagliptin as Prescription Medicines.

DISCUSSION

The following information was considered by MCC and the Committee:

Abatacept

- Abatacept is a co-stimulation modulator, indicated for reducing signs and symptoms, including major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs such as methotrexate or tumour necrosis factor blocking factors.
- Members also noted the following from the Micromedex monograph for abatacept:
    - It may be used alone or with other DMARDs; however, it should not be given with TNF antagonists because of the increased risk of infection. Use with anakinra is also not recommended.
    - Abatacept is given by intravenous infusion over a period of 30 minutes in the following doses: 500 mg for patients weighing less than 60 kg, 750 mg for those weighing 60 to 100 kg, and 1 g for those over 100 kg. The dose is repeated at 2 and 4 weeks, then every 4 weeks thereafter.
    - Abatacept is also being studied for other auto-immune diseases such as multiple sclerosis, psoriasis, and SLE.

Aliskiren

- Aliskiren is an orally active, non-peptide specific renin inhibitor. It is indicated for the treatment of hypertension.
- Members also noted the following from the Micromedex monograph for aliskiren:
    - Aliskiren is an orally active renin inhibitor that is being investigated for use in hypertension and heart failure.

Darunavir

- Darunavir is an inhibitor of HIV-1 protease.
- The proposed indication is for the treatment of HIV infection in antiretroviral treatment experienced adult patients.
- Members also noted the following from the Micromedex monograph for darunavir:

- Adult dose for darunavir is HIV infection, treatment-experienced patients: 600 mg ORALLY twice daily concomitantly with ritonavir ORALLY 100 mg twice daily, with food.
- Safety and efficacy in paediatrics has not been established.

Fosaprepitant

- Fosaprepitant dimeglumine is a prodrug of aprepitant, a substance p/neurokinin (NK1) receptor antagonist.
- The proposed indication is for fosaprepitant in combination with other antiemetic agents, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of:
    1. Highly emetogenic cancer chemotherapy.
    2. Moderately emetogenic cancer chemotherapy.

Lapatinib

- Lapatinib ditosylate is a small molecule reversible tyrosine kinase inhibitor of ErbB1 and ErbB2 receptors. ErbB1 (EGFR) and ErbB2 (HER-2) receptors are frequently over-expressed or altered in human cancers.
- The proposed indication is lapatinib in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbH2 and who have received prior therapy including trastuzumab.

Nepafenac

- Nepafenac is a prodrug which when applied topically to the eye rapidly penetrates the cornea and is converted by ocular tissue hydrolases to amfenac, a potent nonsteriodal anti-inflammatory drug.
- Nepafenac effectively inhibits the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.
- The proposed indication is for the inhibition and treatment of inflammation and pain when dosed beginning one day prior to cataract surgery.
- Members also noted the following from the Micromedex Monograph for nepafenac:
    - An ophthalmic suspension containing nepafenac 0.1% is instilled 3 times daily starting on the day before surgery and continuing for 2 weeks after surgery.

Nilotinib

- Niltotinib is a novel aminopyrimidine, a hightly effective competitive inhibitor of the protein tyrosine kinase activity of Bcr-Abl.

- The proposed indication is the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myeloid leukaemia (CML) in adult patients resistant to or intolerant of at least one prior therapy including imatinib.

Paliperidone

- Paliperidone is a monoaminergic antagonist with a high affinity for serotoninergic and dopaminergic D2 receptors.
- The proposed indication is for the treatment of schizophrenia, including acute treatment and recurrence prevention.
- Members also noted the following from the Micromedex Monograph for paliperidone:
    - The adult dose for paliperidone in schizophrenia with extended-release tablets is initially 6 mg/day orally and may be increased by 3 mg/day increments at intervals of more than 5 days, to a maximum of 12 mg/day.

A Member noted that paliperidone is a metabolite of risperidone which is listed in Appendix K of the SUSDP. The Member stated that the product information for paliperidone listed somnolence as occurring in 6 – 11% of patients and that this is dose related. The Member proposed that this substance should also be included in Appendix K due to the incidence of this side effect.

Ruboxistaurin

- Ruboxistaurin is an isoform-selective inhibitor of protein kinase C β (PKC β), a key factor in the underlying pathophysiology of diabetic microvascular dysfunction and damage.
- The proposed indication is for the treatment of diabetic retinopathy in people with moderate to severe nonproliferative diabetic retinopathy. Arxxant reduces the risk of vision loss in these patients.

Rimexolone

- Rimexolone is a novel corticosteroid that displays limited systemic absorption and local anti-inflammatory activity following topical administration as an eye drop suspension.
- The proposed indication is the treatment of post-operative inflammation following ocular surgery; for the treatment of the palperbral and bulbal conjunctiva, cornea, and anterior segment of the globe.

Vildagliptin

- Vildagliptin belongs to a new class of oral anti-diabetic drugs, known as islet enhancers, and has been developed for the treatment of type 2 diabetes mellitus.

- Members also noted the following from the Micromedex Monograph for vildagliptin:
  - In a study involving 56 patients with type 2 diabetes mellitus given vildagliptin 50 mg once daily by mouth, in addition to existing metformin treatment, the glycosylated haemoglobin value (HbA1c, a measure of long-term blood glucose control), fell from around 7.7% to around 7.1%, whereas HbA1c in 51 patients randomised to placebo did not change.
  - In an extension to the study, 42 vildagliptin-treated and 29 placebo-treated patients were offered treatment for up to 1 year; 32 and 26 patients respectively completed this treatment. HbA1c remained stable in the patients receiving vildagliptin, whereas glycaemic control steadily deteriorated in the placebo-treated patients.

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The Committee agreed to include all these substances in Schedule 4 of the SUSDP on the basis that appropriate use requires medical diagnosis and management and noted that this harmonised the scheduling of these substances with New Zealand. Further, the Committee agreed to include paliperidone in Appendix K of the SUSDP.

Schedule 4 – New Entries

ABATACEPT.

ALISKIREN.

DARUNAVIR.

FOSAPREPITANT.

LAPATINIB.

NEPAFENAC.

NILOTINIB.

PALIPERIDONE.

RIMEXOLONE.

RUBOXISTAURIN.

VILDAGLIPTIN.

Appendix K – New Entry

Paliperidone.

16.2 PROPAMIDINE AND DIBROMOPROPAMIDINE

PURPOSE

The Committee considered the scheduling of propamidine and dibromopropamidine.

BACKGROUND

Propamidine isetionate is an aromatic diamidine antiseptic that is active against Gram-positive bacteria, but less active against Gram-negative bacteria and spore-forming organisms. It also has antifungal properties and is active against Acanthamoeba. Ophthalmic solutions containing 0.1% of propamidine isetionate are used for the treatment of bacterial conjunctivitis and blepharitis.

At the November 1992 DPSSC Meeting, the Committee considered an ADEC review of the quality, safety and efficacy of propamidine/ dibromopropamidine eye drops and eye ointment. The Committee noted the ADEC recommendations regarding the safety and limited efficacy of the substances and recommended that they remain unscheduled. A new Appendix B entry was created for propamidine for external use. Both substances were exempt in Australia as dibromopropamidine was covered by the SUSDP Appendix B entry for propamidine.

The October 2005 NDPSC Meeting noted the MCC June 2005 meeting's proposal that both countries should have a parent entry in Schedule 4 for propamidine and dibromopropamidine and that ophthalmic preparations should be included in Schedule 2. The advice received from the MCC indicated that at its June 2005 meeting, the MCC agreed to include the two compounds in Part I (S4) and the further confirmed that the Pharmacy status of products for ophthalmic use in New Zealand remained appropriate on the grounds that it would not be appropriate for antibacterial eye products to be sold as General Sales medicines. There were no specific safety issues raised by the MCC about either of these substances.

The October 2005 NDPSC Meeting agreed to foreshadow a recommendation that Australia harmonise with the New Zealand scheduling for propamidine and dibromopropamidine. The October 2005 NDPSC Meeting also noted what appeared to be an inappropriate 'reason for entry' for propamidine in Appendix B, i.e. for industrial use only, while the 'area of use' specified was 'Human therapeutic use – Eye Drops'.

At the February 2006 NDPSC Meeting, the Committee considered the harmonisation proposal put forward by the MCC. Members did not support the option of listing a parent entry in S4 for propamidine and dibromopropamidine in order to harmonise with New

Zealand while exempting only ophthalmic preparations. Members maintained the view that the exemption provided for ophthalmic preparations in Appendix B of the SUSDP did not imply that other preparations were scheduled. Members also recalled that harmonisation should occur on the least restrictive schedule and this would require New Zealand to reclassify the entries for propamidine and dibromopropamidine to General Sales. The Committee agreed to recommend to New Zealand that they consider harmonising with Australia on the scheduling status of propamidine and dibrompropamidine. At this Meeting, Members further agreed to include a new Appendix B entry for dibromopropamidine and to correct the reason for listing to 'low toxicity'. 'a' in the Appendix B entry relates to low toxicity and '6.10' refers to human therapeutic use eye drops.

DISCUSSION

At their February 2007 Meeting, the MCC considered a submission for the rescheduling of propamidine and dibromopropamidine eye drops and eye ointment from Pharmacy to General Sale. The MCC also noted that the NDPSC had recommended that New Zealand harmonise with Australia on the scheduling of these substances. The MCC made the following considerations:

- The substances were safe for use in treating minor conditions and the toxicity profile was suitable for a general sale listing.
- None the less, the MCC felt strongly that it was inappropriate to treat ocular infections at a general sale level as consumers should have access to pharmacist advice for substances used for eye infections and this advice would not be available in general sale outlets. Members also noted that there were guidelines in place for pharmacy assistants dealing with eye conditions and for referring patients to pharmacists.
- Members felt that the potential risk of inappropriate use supported their view that pharmacist advice should be available to consumers at point of sale for these products.
- Thus, the MCC felt that the increase in risk to consumers from changing the scheduling of propamidine and dibromopropamidine (which may lead to inappropriate use of the substances), outweighed any potential benefit to them and thus the current Pharmacy-only classification should be maintained.
- Given this, the MCC recommended that the NDPSC harmonise with New Zealand on the scheduling of propamidine and dibromopropamidine.

There are currently three products on the Australian Register of Therapeutic Goods (ARTG) which contain propamidine or dibromopropamidine. XXXXX containing 1mg/ mL propamidine and XXXXX containing 1.5mg/ g dibromopropamidine.

XXXXX provided a pre-Meeting XXXXX in which XXXXX stated that, based on the toxicity of the substances, exemption from scheduling is logical. XXXXX also stated, however, that the labelling for these products was currently insufficient as it lacked information directing the consumer to seek medical attention for certain circumstances. XXXXX provided submissions supporting this.

A Member stated that this is a harmonisation issue but also an opportunity to schedule the substances more appropriately. The Member stated that while the substances may be very safe, the indication and patterns of use do require the patient to have access to the advice of a pharmacist if needed. The Member also noted that all of the products on the ARTG are registered products, so the regulatory impact of including the substances in Schedule 2 would be negligible. Members discussed that it was likely that most of the sales of these substances was through pharmacies and, indeed, the Committee was not sure whether the products were being sold in supermarkets at all.

A Member stated that there was a registered topical formulation which was not indicated for ocular infections and that the proposed schedule entry would make this an S4 substance and that there was no evidence based justification for this. Another Member stated that the proposed schedule entry could be amended to either exempt topical use or include it in Schedule 2. Members noted that the non-occular product was not actively marketed in Australia and that no pre-Meeting response had been received from the sponsor on this matter. It was noted that a solution to this issue may be to write to the sponsor of the product and invite them to comment on the issue.

A Member recalled that the original New Zealand scheduling for the substances was Schedule 2, but under the principles of Trans-Tasman Harmonisation it was decided that a parent entry should be included in Schedule 4 just in case a formulation other than an eye drop was brought to market. Members discussed this and noted that the proposed schedule entry would capture other uses such as oral use in Schedule 4. Members agreed that this was appropriate given that there was no safety data on other uses than ocular and topical of the substance.

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The Committee agreed to include propamidine and dibromopropamidine for ophthalmic use in Schedule 2 and for all other use in Schedule 4 of the SUSDP due to concerns regarding the appropriateness of consumers treating ocular infections without access to pharmacist advice if required. The Committee also noted that this would harmonise the scheduling of propamidine and dibromopropamidine with New Zealand.

Schedule 2 – New entry

PROPAMIDINE for ophthalmic use.

DIBROMOPROPAMIDINE for ophthalmic use.

Schedule 4 – New entry

PROPAMIDINE for therapeutic use **except** where included in other schedules.

DIBROMOPROPAMIDINE for therapeutic use **except** where included in other schedules.

Appendix B – Delete entry

Propamidine	Nov 1992	a	6.10
Dibromopropamidine	Feb 2006	a	6.10

16.3 BORON / BORIC ACID

PURPOSE

The Committee consider the scheduling of boron (including boric acid and borax).

BACKGROUND

Boron for human therapeutic use is Schedule 4 (with a number of exemptions), while non human therapeutic use of boric acid and borax is Schedule 5. These scheduling positions have evolved over many meetings, where the major concern in human therapeutic use was oral and dermal toxicity – in particular boric acid and borax when used as antiseptics, and the dermal use of boron compounds on infants. The inclusion of boron in Schedule 4 was primarily intended to restrict these uses.

The February 2006 NDPSC Meeting noted the unharmonised status of boron/boric acid and noted:

- The New Zealand boric acid entry evolved from the need to provide guidance to industry in terms of acceptable product strengths and indications when the issue of toxicity emerged from the use of high strength boron products for the treatment of nappy rash in babies under occlusive conditions.
- There were no adverse reactions associated with boron reported in Australia or New Zealand since the year 2000.
- That an assessment of the potential regulatory impact of the proposal to harmonise the scheduling of boron with New Zealand was appropriate. The Members were advised:
    - The May and August 2001 NDPSC Meetings agreed to revise the boron Schedule 4 entry to exempt a daily oral dose of 3 mg and to exempt dermal preparations containing ≤ 0.35 % to harmonise with the New Zealand scheduling of dermal

use. However, the Committee was not prepared to harmonise on the other use patterns. This outcome was recommended to MCC for consideration.

- A review of products on New Zealand's SMARTI yielded 7 eye preparations (5 General Sale (GS) and 2 Pharmacy Only) and one GS vaginal gel containing 9 mg/g boric acid. These products listed boric acid as "other" ingredient which suggested that boric acid may be an excipient these preparations. The concentrations of boric acid in the eye preparations ranged between 6-18 mg/mL. Eye preparations containing boron as active ingredient at any concentration were Schedule 4 in Australia but boron when present as an excipient in medicines was excluded. Furthermore, boron in dietary supplements in New Zealand could not be assessed for regulatory impact as there was no database for such products.
- From an Australian perspective, potentially affected products would move to less restrictive schedules if the Committee harmonised with New Zealand (except antifungal preparations which would become subject to concentration cut-offs). The expected regulatory impact on Australian products would be minimal.

- A Member advised that New Zealand only had products containing boric acid and that boron was not listed as an ingredient in medicines. In contrast, Australian products included as ingredient either elemental boron or boric acid. The Member pointed out that the current scheduling of boron in the SUSDP excluded excipients from the requirements of scheduling and that this may need to be reviewed on the basis of the substance's toxicity.

The February 2006 NDPSC Meeting agreed to recommend that New Zealand consider harmonising with the scheduling of boron and for MCC to consider making a recommendation to the NDPSC to harmonise on an appropriate nomenclature for boron.

DISCUSSION

The 36th MCC Meeting considered a number of harmonisation recommendations from the NDPSC including the February 2006 recommendation regarding boron. The MCC decided that a change to the classification of boron should not be made at this point. The following course of action was agreed upon:

- The NDPSC should be consulted over a suggested nomenclature to be used for the boron Schedule 4 schedule entry.
- The NDPSC should be recommended to use the [*asserted*] normal cascade effect for the Schedule 4 schedule entry.
- The NDPSC should be recommended to remove the exemption for antifungal medicines from the Schedule 4 schedule entry for boron.
- MCC consultation should occur with the complementary medicines sector through the normal process on the Medsafe website to establish the nature and strength of products already on the New Zealand market. If products were available containing

more than the proposed cut-off points of 3 mg per recommended maximum daily dose for internal use or 0.35% for dermal use, sponsor companies should be invited by MCC to provide safety data to support these higher doses or concentrations.

- The Pharmaceutical Society should be approached by MCC to inquire whether or not boron/borax was sold for non–therapeutic purposes. The matter should return to the MCC when the above course of action had been completed.

Members also noted the following from the MCC minutes:

- While the SUSDP [*human therapeutic*] entries referred to boron, the New Zealand schedule classified boron as boric acid. MCC considered that "boron, including boric acid and borax" should cover all possibilities.
- MCC considered the cut-off for exemption from scheduling for products used in complementary medicines, noting that the February 2006 NDPSC Meeting recommended that the MCC should harmonise with the Schedule 4 entry for boron.
- MCC asserted that the Schedule 4 boron entry was atypical in that all the inclusions were listed in the entry. MCC also asserted that this had obviously been designed to prohibit products available at the time the entry was made and was contrary to the usual SUSDP entries which listed exclusions rather than inclusions. MCC agreed, for consistency, to recommend NDPSC use the normal cascade effect for the Schedule 4 boron entry and list only those medicines which were excluded from Schedule 4 status. [Members noted that there are current both inclusive and exclusive entries in the SUSDP, and although the exclusive entries predominate, there has been no policy against inclusive entries.]
- It was suggested that the following Schedule 4 entry or words of similar meaning should cover all exigencies:

"……**except**:

(a) for internal use in medicines containing X mg or less per recommended daily dose;

(b) for dermal use in medicines containing X per cent or less; or

(c) when present as an excipient."

[The Committee noted that this wording did not capture the full intent of the existing entry. Members considered alternative wording which captured the existing requirements, including no exclusion for dusting powders when for paediatric use.]

- MCC also questioned the need for an exemption for antifungal preparations. MCC agreed that, not only were there better antifungal products available, but also that absorption of boron would occur through broken skin and that this use should be

discouraged. It was recommended that NDPSC consider removing the exemption for the use of boron as an antifungal from the schedule entry.

- MCC discussed the recommended cut-off points (3 mg per recommended daily dose for internal use; 0.35% for dermal use) and concluded that MCC needed to know what products were available in New Zealand. It was noted that data to hand seemed to suggest that 10-18 milligrams of boron per day could be taken for life without any toxic effects. The minimum toxic dose appeared to be approximately 3.6 g for children and 15 g for adults. In view of these figures MCC felt that the recommended cut-off points in the Australian schedule might be unnecessarily conservative. It was agreed that further information should be sought before adopting these cut-off points.

Members noted the following from the August 2001 NDPSC consideration:

- The Committee amended the Schedule 4 boron entry at the May 2001 NDPSC Meeting to exempt internal preparations containing 3 mg per recommended daily dose on the basis that this provided a suitable margin for dietary intake of boron, covered existing products and would not exceed the tolerable daily intake (TDI) (see discussion of toxicity from the May 2001 NDPSC Meeting set out below).
- Post-meeting correspondence drew attention to the conclusions regarding the TDI of the US FDA (0.4mg/kg/day) and EU Expert Committee on vitamins and minerals who accepted the same TDI as the US and quoted the WHO safe and acceptable intake range for adults of 1-13 mg/day. A stakeholder noted that the proposed maximum daily intake of 3 mg/day was very low by comparison with these values and requested that the cut-off be set at 10 mg/day for the maximum daily adult dose.
- In relation to the 3 mg recommended maximum daily dose, the Committee was reminded that the TDI was derived from developmental effects in a rat study using a 25 fold safety factor. The Committee agreed that this was a very low safety factor for this kind toxicological end-point and that limiting the maximum daily dose to 3 mg had provided an additional margin of safety.
- It was noted that the Committee had moved from a position of not exempting any non-excipient use of boron in internal preparations, to exempting preparations up to a maximum recommended daily dose of 3 mg boron. This recognised the existing products on the market while maintaining a reasonable safety factor for products that were of doubtful efficacy in relation to the claims made for boron.
- It was not considered appropriate to support doses close to a TDI when that was related to a possible developmental effect. This was in contrast to the margin of safety that would be associated with a no-effect level and establishment of an ADI.
- The Committee agreed that 0.35% boron was the appropriate figure for harmonising with the NZ exemption of external products containing 2% or less of boric acid. The Committee did not agree to extend the exemption for boron in internal preparations as this would erode the safety factor for a toxicological end-point based on developmental effects.

Members were also advised that the following toxicity data was considered at the May 2001 NDPSC Meeting:

- The Committee discussed three reviews on boron toxicity, IPCS Environmental Health Criteria (1998), National Academy of Sciences (December 2000), and the Expert Review on Vitamins and Minerals (1999), and found that all three were consistent in their findings. Members noted with interest that boron, which exists in the form of borates and boric acid, had a TDI of 0.4 mg/kg bw/day, set by the IPCS (1998). The TDI was derived from a NOAEL of 9.6 mg/kg bw/kg for decreased foetal body weight in a rat developmental study and using a 25-fold safety factor. The TDI equated to 28 mg/day for a 70 kg person, while the estimated mean dietary intake of boron was around 1.2 mg/day, which was low in comparison to the TDI.
- The LD_{50} in laboratory animals had been reported in the range: 3.5 – 4.5 g/kg bw.
- The LOAEL for the rat development study was 13.3 mg/kg bw/day.
- Potential lethal dose for adults had been reported to be 15-20 g/day and 3-6 g/day for infants. Maximum drinking water level for boron in the UK is 2 mg/L.
- According to case reports of poisonings and accidental ingestions of boric acid and borax, these compounds exhibit low toxicity. There have been no reports of boron toxicity in lactating women.

Pre-meeting comments were received from XXXXX and XXXXX reserving the right to comment further. A pre-meeting comment from XXXXX noted the MCC discussions related to the human therapeutic use of the substances and understood that the Committee consideration was only with regard to human therapeutic uses. Should non-therapeutic uses be considered then it would be pleased to provide additional information.

The Committee was advised that it was MCC's intention to use the above recommendations to start a dialogue about an acceptable format for a Schedule 4 entry. There had been no expectation from the MCC that the cut-off issue would be resolved at the June 2007 NDPSC Meeting. While MCC had yet to come to a conclusion regarding a daily dose exemption cut-off, it did note some suggestions that 9 mg would be more appropriate.

Members were also advised that the main issue with the current 3 mg exemption cut-off was the additional safety factor applied by the Committee in 2001. Members generally agreed that MCC would need to establish a convincing rebuttal case against the 2001 decision if the Committee was to consider changing this cut-off. A Member noted that the additional safety margin accounted for exposure to boron from multiple sources, including diet and complementary medicines, and these other sources needed to be kept in mind. Another Member noted that there was also the possibility of accumulation, given boron's diphasic excretion pattern.

Members agreed that consideration of the scheduling of boron should be deferred until MCC had reached agreement on a position regarding an exemption cut-off level. With regard to the nomenclature and format of the current Schedule 4 entry, the Committee agreed to indicate to MCC that the following format was appropriate (noting that the issue of the exemption cut-off remained unresolved):

BORON, including boric acid and borax, for human therapeutic use **except**:

(a) in preparations for internal use containing **X** mg or less per recommended daily dose;

(b) in antifungal preparations for dermal use;

(c) in other preparations for dermal use containing 0.35 per cent or less boron which are not dusting powders for paediatric use; or

(d) when present as an excipient.

Members noted that the above format would broaden the existing inclusive entry and could capture some previously unscheduled human therapeutic uses of boron i.e. topical applications such as use on the eye.

OUTCOME

The Committee agreed that consideration of the scheduling of boron should be deferred pending information coming from New Zealand about whether it will be proposing a new exemption cut-off, and the reasons for any such recommendation.

16.4 CHOLINE SALICYLATE

PURPOSE

The Committee considered the scheduling of choline salicylate.

BACKGROUND

Choline salicylate is a salicylic acid derivative used in the treatment of pain and fever, and in the management of rheumatic disorders. It is also used as a local analgesic and solutions containing up to about 20% choline salicylate are used in ear disorders such as the relief of pain in otitis media and externa. An 8.7% gel formula is used for treating lesions of the mouth. In terms of salicylate content, choline salicylate 435 mg is equivalent to about 325 mg of aspirin.

Choline salicylate itself has never been considered for scheduling by the Committee as it is a derivative of salicylic acid and therefore captured by the SUSDP entry for that substance.

The February 2001 NDPSC Meeting, based on harmonisation and safety concerns about high concentration salicylic acid preparations, included a new Schedule 3 entry for dermal use preparations of salicylic acid containing more than 40% of the substance.

At the June 2006 NDPSC Meeting, it was recommended to New Zealand that they harmonise on the Schedule 3 for salicylic acid by changing the word 'external' in their Restricted Medicine entry to 'dermal'.

DISCUSSION

The February 2007 MCC Meeting considered the NDPSC recommendation to amend the wording of its Restricted entry for salicylic acid. The MCC agreed to this, however noted that this would inadvertently affect a number of oral gel products which contained the salicylic acid derivative choline salicylate. The MCC further noted that choline salicylate is a recommended INN of its own and that, in New Zealand, unlike Australia, derivatives of substances are not covered by the parent entry.

Given this, the MCC considered that a new schedule entry for choline salicylate should be introduced which would capture as a prescription medicine any preparations containing more than 10% of the substance and specifically exempt any preparations containing less than 10% of choline salicylate in pack sizes of 15 grams or less. The 10% cut-off limit was considered to be appropriate for general sale given the concentration of choline salicylate in current general sale products. The MCC recommended to the NDPSC that they adopt this scheduling of choline salicylate.

The MCC's definition of 'external use', as per the *Medicines Regulations 1984,* is as follows:

> *"For external use, in relation to any medicine or related product, means for application to the anal canal, ear, eye, mucosa of the mouth, nose, skin, teeth, throat, or vagina, where local action only is required and where extensive systemic absorption will not occur; but nothing in these regulations relating to medicines or related products intended for external use shall apply to nasal drops, nasal inhalations, nasal sprays, teething applications, throat lozenges, throat pastilles, throat sprays, or throat tablets."*

However, the definition of external in the SUSDP is:

"External in relation to the use of a poison means application in the ears, eyes or nose or to a body surface other than in the mouth, rectum, vagina, urethra or other body orifice."

Thus, the two definitions differ quite markedly as the New Zealand definition of external use includes the mouth, rectum and vagina, whereas the SUSDP definition specifically excludes these.

The MCC does not have a current definition of dermal, however in the draft SUSMP the definition of dermal is:

*"**"Dermal use"** means application to the skin primarily for localised effect."*

This is essentially the same as the current SUSDP definition of dermal:

"Application to the skin, primarily for localised effect."

XXXXX provided a submission in which XXXXX stated that choline salicylate gels in current strengths and pack sizes should remain unscheduled. XXXXX provided submissions supporting this.

XXXXX provided a pre-Meeting submission in which XXXXX stated that the current scheduling of choline salicylate in Australia remained appropriate and there were a number of issues which need to be addressed before looking at a new entry for choline salicylate. The main points were:

- XXXXX made comments about the MCC scheduling of salicylic acid and stated that this had lead to the entries being unharmonised between the two countries. XXXXX discussed the differences between definitions in both countries, noting that in Australia 'external' as defined in the SUSDP specifically exempts application in the mouth, whereas in New Zealand the definition includes application to the oral mucosa. XXXXX stated that the principle issue should be the harmonisation of the definition of this term between the countries. XXXXX also stated that there should be uniformity in the application of terms such as dermal and external in schedule entries and note examples of where this differs. It was noted by the Committee that these comments are outside the scope of the gazetted item for consideration and the SUSMP will have harmonised definitions for these terms.
- XXXXX noted that derivatives of substances were covered by the parent entry in the SUSDP, but that this is not the case in New Zealand. XXXXX felt that this was a primary issue which needs to be resolved in the interests of harmonisation and that the approach taken in the SUSDP should be adopted. Again the Committee noted that this issue would be resolved with the introduction of the SUSMP.
- Given this, XXXXX opposed the MCC's proposal for a separate schedule entry for choline salicylate. XXXXX felt that the MCC's decision on the matter of pack size and cut-off for the schedule entry was not evidence based and there was no safety data showing such limits were warranted. XXXXX stated that given the 40% exemption for salicylic acid, the 10% cut-off for choline salicylate needed to be reviewed by the MCC. XXXXX also stated that the imposition of a pack size moved

away from harmonisation and would serve to deny consumers access to value packs in the future. XXXXX also stated that there was no evidence that choline salicylate warranted being a prescription only medication and that any entries in New Zealand should be limited to GSL and Restricted as was the case for salicylic acid.

- Lastly, given the impact on harmonisation issues, XXXXX requested that NDPSC raise this issue with MCC for further consideration and that, given choline salicylate was already captured as a derivative in Australia, there should be no separate entry for it in the SUSDP.

XXXXX provided a pre-Meeting submission stating XXXXX opposition to the inclusion of a new schedule entry for choline salicylate with a cut-off of 10% and a pack size of 15 grams. The main points were:

- XXXXX noted that XXXXX had written to the MCC regarding their schedule entry for salicylic acid and the harmonisation issues this has raised. XXXXX also stated that the issue of the differences in definitions of dermal and external between the two countries should be addressed in order to progress scheduling harmonisation. XXXXX therefore urged both Committees to review these definitions.
- XXXXX stated that the consideration by MCC of choline salicylate was not evidence based and no data was presented to support the 10% cut-off and 15 gram pack size limits. It was further stated that, given the GSL cut-off for salicylic acid is 40%, the cut-off for choline salicylate should be reviewed.
- XXXXX felt that the recommendation to include an entry for choline salicylate in the SUSDP moved away from the principle of the schedule entry for a parent substance including all salts and derivatives of a substance unless specifically stated otherwise.

A Member stated that, as the New Zealand definition of external is enshrined in legislation it cannot to be easily altered and thus cannot be used in the schedule entry as recommended by the NDPSC. The Member also noted that this issue and the lack of capture of derivatives by New Zealand Medicines Schedule parent entries would be resolved when the SUSMP came online with the creation of ANZTPA.

Members agreed that, given the capture of choline salicylate by the parent entry of salicylic acid in the SUSDP and New Zealand's schedule entry for choline salicylate, the outcome was that Australia and New Zealand were essentially harmonised on the scheduling of this substance.

OUTCOME

The Committee agreed that the current scheduling of choline salicylate remained appropriate as it is captured by the parent entry for salicylic acid. The Committee also noted that Australia and New Zealand were essentially harmonised on the scheduling of this substance.

16.5 NAPROXEN AND MEFENAMIC ACID

PURPOSE

The Committee considered applying maximum daily dose restrictions to the Schedule 2 entries for naproxen and mefenamic acid.

BACKGROUND

Naproxen

Naproxen is a non-steroidal anti-inflammatory drug (NSAID), which is able to inhibit cyclo-oxygenase, an enzyme involved in the production of prostaglandins. Prostaglandins are able to exert a variety of effects on the inflammatory process, including the production of fever. Naproxen is highly soluble in water and almost completely absorbed in the GI tract, with therapeutic levels being attained within 20 minutes and peak levels within 1-2 hours.

Naproxen was included in Schedule 4 at the November 1977 meeting of the Committee. At the February 1983 meeting the rescheduling of naproxen to Schedule 3 for the treatment of spasmodic dysmenorrhoea was approved. A request in July 1987 to reschedule to Schedule 2 naproxen in small pack sizes for short-term indications was rejected. Following consideration of a submission at the August 1989 Meeting, the Committee agreed to Schedule 2 for naproxen for primary dysmenorrhoea. However, an application for S2 for other indications was rejected at the November 1989 meeting.

The November 1998 meeting of NDPSC considered a rescheduling application from XXXXX to reschedule naproxen sodium 220 mg tablets in packs of 10 to Schedule 2 without indication restriction. The Committee considered that Schedule 3 was more appropriate for naproxen, in small packs sizes, though it did increase the pack size permitted in Schedule 2 for the treatment of dysmenorrhoea from 12 to 20. At the November 1999 Meeting, the Committee agreed to extend the Schedule 2 indication for naproxen to include minor analgesia and increased the maximum pack size to 30 dosage units.

The August 2001 NDPSC Meeting considered a proposal to exempt from scheduling naproxen 250mg or less per dosage unit, in packs of 24 or less dosage units, for the short-term treatment of dysmenorrhoea. At this Meeting the Committee agreed that naproxen was appropriately scheduled in Schedule 2 for the treatment of dysmenorrhoea on the basis that access to professional advice was required. The Committee felt that this was necessary to help the patient differentiate between primary and secondary dysmenorrhoea and advise on potential drug/drug and drug/disease interactions when requested by the patient.

Mefenamic Acid

Mefenamic acid, an anthranilic acid derivative, is an NSAID, although its anti-inflammatory properties are considered to be minor. The precise mechanism of action is not known, however in animal studies, mefenamic acid inhibits prostaglandin synthesis and competes for binding at the prostaglandin receptor site. It is used in mild to moderate pain including headache, dental pain, postoperative and postpartum pain, and dysmenorrhoea, in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis, and in menorrhagia.

Mefenamic acid was included in Schedule 4 at the November 1963 meeting of the Committee and it was rescheduled, when in packs of 30 capsules or less and labelled for the treatment of spasmodic dysmenorrhea, to the 'new' Schedule 3 at the February 1979 Meeting.

The November 1986 DPSSC Meeting rejected a proposal to include mefenamic acid for the treatment of dysmenorrhoea in Schedule 2 of the SUSDP on the basis of concerns regarding the safety of the substance and the need for pharmacist advice, and potential referral to a medical practitioner in chronic users, for the patient. A further submission in July 1987 to reschedule mefenamic acid in small pack sizes for the treatment of dysmenorrhoea to Schedule 2 was also rejected.

At the February 1991 DPSSC Meeting, the Committee considered a new submission to reschedule packs containing 30 dosage units or less of mefenamic acid for the treatment of dysmenorrhoea to Schedule 2. After consideration, the Committee agreed that Schedule 2 was appropriate for 'mefenamic acid when in packs of 30 or less dosage units for use in dysmenorrhoea.'

At the February 1999 NDPSC Meeting the wording of the Schedule 2 entry for mefenamic acid was amended slightly to "Mefenamic acid in divided preparations for oral use in packs of 30 or less dosage units for the treatment of dysmenorrhoea" in order to harmonise scheduling with New Zealand. This amendment was confirmed at the November 1999 NDPSC Meeting.

General Considerations:

During all of these considerations for both substances there was no discussion minuted of the possibility of a maximum daily dose restriction in the Schedule 2 entries.

The current maximum daily dose stated in the Schedule 2 entry for diclofenac is 75mg. This is half the maximum recommended daily dose as per the Martindale monograph. It was noted that at the February 2005 NDPSC Meeting the Committee derived the 75mg maximum daily dose for diclofenac from clinical trial data presented XXXXX as part of the evaluation process for the registering of a 12.5mg Schedule 2 diclofenac presentation. This data supported an acceptable safety profile of diclofenac 12.5mg at a daily dose of

up to 75mg and the Committee felt that this warranted its inclusion, with the proviso of the maximum daily dose, in Schedule 2 of the SUSDP. The Committee further noted that this would harmonise the scheduling of diclofenac 12.5mg with New Zealand.

The current maximum daily dose stated in the Schedule 2 entry for ibuprofen is 1200mg. This is half the maximum recommended daily dose as per the Martindale monograph. The reasons were not elucidated to as to why the 1200mg cut-off for ibuprofen was initially included in the schedule entry. This cut-off was then carried over to the new Schedule 2 entry.

DISCUSSION

As part of the discussion of the scheduling of diclofenac at the February 2007 (36th) MCC Meeting, it was noted that neither naproxen nor mefenamic acid had a maximum daily dose restriction applied to their Schedule 2 entries, in comparison to the diclofenac and ibuprofen Schedule 2 entries. MCC Members felt that this inconsistency should be addressed, as adverse reactions for this class of substance were often dose related and also for consistency with the other Schedule 2 entries. MCC stated that they would consult on this issue and consider it at their next meeting. MCC also recommended to the NDPSC that it should consider applying such a maximum daily dose to these entries.

XXXXX provided a pre-Meeting comment in which XXXXX stated that adverse events, particularly gastrointestinal and renal, with NSAIDs as a class were dose-related. XXXXX stated that, given this, it would appear reasonable to set a maximum daily dose guided by the OTC approval process as it would help to minimise the risk of adverse events.

The XXXXX provided a pre-Meeting submission in which XXXXX supplied the prescription Product Information (PI) documents for naproxen and mefenamic acid. The PI for naproxen stated that the maximum daily dose for all indications should not exceed 1250mg. The PI for mefenamic acid stated that, for the treatment of dysmenorrhea, 500mg should be taken three times a day. This equates to a maximum daily dose of 1500mg.

Advice was received by the XXXXX regarding the setting of maximum daily doses for the Schedule 2 entries for naproxen and mefenamic acid. The following points were made:

- There was no current labelling order (i.e., RASML or TGO 69) which stipulated a maximum daily dose for either substance as Schedule 2 medicines and further, as Schedule 2 medicines, neither substance required a PI or CMI document.
- XXXXX noted that the recent TGA review of NSAIDs (including naproxen and mefenamic acid) found that although the short-term use of non-selective NSAIDs at OTC doses did not appear to be related to an increased risk of serious cardiovascular

(CV) events, OTC doses of NSAIDs administered for long periods of time were associated with increased CV risk. Further, the review also noted that serious, life-threatening gastrointestinal events such as ulceration, bleeding and perforation were well-documented with NSAID treatment.

- XXXXX was currently considering strengthening the RASML statement "Unless a doctor has told you to, don't use [this product/ *insert name of product*] for more than a few days at a time".
- Given these factors, along with the fact that both ibuprofen and diclofenac have S2 maximum daily doses, it was appropriate for naproxen and mefenamic acid have maximum daily doses stipulated.
- XXXXX referred to the maximum daily doses for naproxen and mefenamic acid as stated by Martindale (1250mg and 1500mg respectively) and suggested that these were appropriate for the S2 maximum daily dose cut-offs for Schedule 2 as this would help ensure the use of the lowest dose for the shortest time.

XXXXX provided a pre-Meeting submission in which XXXXX supported a cut-off being included in the Schedule 2 entries for naproxen and mefenamic acid as this was consistent with other Schedule 2 NSAID entries. XXXXX stated that, on the basis of maximum recommended daily doses, the cut-offs should be 1500mg or less for mefenamic acid and 1250mg or less for naproxen.

XXXXX provided a pre-Meeting comment in which XXXXX proposed that the maximum daily dose of naproxen be 5 tablets, which is equivalent to 1250mg naproxen. XXXXX noted that this was based on the dosing instructions approved by the TGA.

The current (as per PI documents) approved dosing for diclofenac as a Schedule 2 substance is 2 tablets (25 mg) initially, then 1 – 2 tablets every 4 – 6 hours up to maximum of 6 tablets/ day (75mg). For S2 ibuprofen it is 400 – 800mg initially, then 400mg every 4 – 6 hours to a maximum of 1200mg/ day. For S2 mefenamic acid the dosage instructions are 2 capsules (500mg) 3 times/ day. For S2 naproxen the instructions state 500mg initially, then 250mg every 6 – 8 hours with a daily maximum of 1250mg.

A Member stated that it was unnecessary for daily dose limits to be included in schedule entries are these were a matter for and were set by the regulator. The Member suggested that the Committee may wish to look at removing the daily dose requirements from the schedule entries for ibuprofen and diclofenac for consistency. Members discussed this and agreed that there was no scientific information that would indicate an alteration of the Schedule 2 entries for diclofenac and ibuprofen was required.

Members discussed that the maximum daily doses included in the Schedule 2 entries for ibuprofen and diclofenac were half that stated in the Martindale while the doses proposed for mefenamic acid and naproxen were the full doses stated in the Martindale. The Committee considered whether, given this, that the proposed Schedule 2 entries for naproxen and mefenamic acid should state a daily dose which was half the maximum

recommended. However, the fact was discussed that the daily doses for ibuprofen and diclofenac were not just arbitrarily set at half the maximum, rather these were set after the Committee had considered a large amount of scientific data about the risks and benefits of including the substances in Schedule 2. It was pointed out that the Committee did not have to schedule consistently on half of the Martindale dose, rather they had to schedule on the science.

The Committee recalled that both naproxen and mefenamic acid were first down-scheduled for dysmenorrhoea and that this patient group were in a different risk category for use as it was only a short-term indication, therefore they were less likely to suffer adverse effects. It was further recalled that for naproxen the indications had been broadened and included some longer-term indications but the maximum daily dose had not been altered to reflect this and perhaps therefore the dysmenorrhoea dose may not be appropriate for the other indications. A number of Members stated that there had been no scientific data presented to the Committee apart from the Martindale which the Committee could use to set cut-offs for either naproxen or mefenamic acid and that to do so in the absence of full data would be unlikely to be justifiable. It was also noted that the Committee had not received any data regarding problems with these substances.

A Member stated that when the sponsor of naproxen sought an extension of indications from the OTC Medicines Section, it was likely that they had put forward data regarding side effects and maximum daily doses. The Committee discussed this and felt that the regulator would have assessed this data in allowing the current maximum daily doses to be set as part of their registered indications. It was felt that that there was no requirement for the Committee to pursue consistency for consistency's sake and, further, that there was no requirement under Section 52E for this to occur.

OUTCOME

The Committee agreed that the current scheduling of naproxen and mefenamic acid remained appropriate given that the setting of maximum daily doses was an issue for the regulator, that there was no scientific evidence presented requiring a change to the schedule entry and there was no requirement under Section 52E of the *Therapeutic Goods Act 1989* which required consistency across a class of schedule entries.

16.6 MERCURIC OXIDE / MERCURY

PURPOSE

The Committee considered the scheduling of mercuric oxide.

BACKGROUND

The October 2006 NDPSC Meeting noted that there were no Schedule 2 mercuric oxide products registered in either Australia or New Zealand and agreed, on the basis of

accepted policy, to replace the Schedule 2 mercuric oxide entry with a Schedule 4 parent entry for mercuric oxide when for human therapeutic use. The Committee also agreed to recommend to New Zealand that it harmonise with this decision.

DISCUSSION

The 36th MCC Meeting considered a number of harmonisation recommendations from the NDPSC including the October 2006 recommendation regarding mercuric oxide. Members noted the following from the MCC minutes:

- Mercuric oxide was currently a pharmacy-only medicine in both countries when for ophthalmic use [*prior to the October 2006 NDPSC decision*]. However, there were no longer any products registered in either country.
- If mercuric oxide were reclassified to prescription medicine for all uses it would be covered by the entry for mercury and a separate entry would no longer be required.
- MCC agreed that the New Zealand pharmacy-only entry for mercuric oxide should be removed from the schedule. MCC also recommended that the NDPSC be advised that there was no longer any need for a separate schedule entry for mercuric oxide.

Members noted that there are Schedule 2, 4 and 7 entries for mercury, with both the Schedule 2 and 4 entries capturing human therapeutic use. The Schedule 4 mercury entry already captures the cosmetic use and non-human therapeutic use patterns of mercuric oxide.

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The Committee agreed:

- Mercuric oxide is a derivative of mercury.
- To delete the mercuric oxide Schedule 4 entry as the risks associated with mercuric oxide will be appropriately controlled by the mercury scheduling cascade.

Schedule 4 – Amendment

MERCURIC OXIDE – Delete entry.

17. MINUTES OF THE ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (ADRAC)

Nil items.

18. MINUTES OF THE MEDICAL DEVICE EVALUATION COMMITTEE (MDEC)

Nil items.

19. [ITEMS DELETED]

20. GAZETTAL NOTICES

The Committee noted:

- the pre-June 2007 Gazette Notices No.16 of 24 April 2007 and No.S88 of 9 May 2007; and
- the post-February 2007 Gazette Notice No.14 of 11 April 2007.

21. AMENDMENTS TO THE SUSDP

21.1 [ITEM DELETED]

21.2 EDITORIALS AND ERRATA – APPROPRIATE AUTHORITY DEFINITION, DROTRECOGIN, HYDROCORTISONE, NICOTINE, INDOXACARB, MALDISON / MALATHION, METHYLANDROSTANOLONE, NICOTINIC ACID.

PURPOSE

The Committee:

- noted the editorial amendments incorporated into the consolidation of SUSDP 22 relating to South Australia's appropriate authority;
- considered editorial amendments to nicotine, indoxacarb, maldison, nicotinic acid, drotecogin, and methylandrostanolone; and
- considered varying the February 2007 NDPSC decision (2007/49-13) regarding hydrocortisone.

DISCUSSION

Appropriate authority – The contact details for South Australia had recently been amended, splitting the responsibility for labelling and scheduling enquiries into a drugs and a poisons area. The Secretariat contacted XXXXX to confirm whether there should be any consequential amendment to the SA "appropriate authority" definition in Part 1 1.(1)(e). XXXXX advised that the "appropriate authority" should be listed as "the Chief

Executive of the Department of Health". The SUSDP 22 consolidation was amended to reflect this change.

Nicotine – The June 2004 NDPSC Meeting agreed to delete nicotine from Schedule 3 of the SUSDP but overlooked the Appendix H listing for nicotine. The Committee agreed to delete the nicotine Appendix H listing.

Indoxacarb – In response to concerns regarding the prototype presentation of an indoxacarb product (presented in XXXXX which might have been attractive to children), the June 2006 NDPSC Meeting agreed to include a cut-off from the Schedule 6 indoxacarb entry to Schedule 5 for ≤ 1% indoxacarb (when packed in child resistant packaging (CRP)). This decision was confirmed at the October 2006 NDPSC Meeting. Subsequently, a meeting was held between XXXXX and XXXXX in which XXXXX demonstrated the final presentation of the product. This presentation was markedly different and could not be easily accessed by children. It was also noted that there was no Australian Standard for CRP for such devices and hence the conditions of the current Schedule 5 entry could not be met. A Member also noted that the regulator would consider the appropriateness of the packaging as part of the registration process. The Committee agreed, given that the concerns which led to the wording for the Schedule 5 entry had been allayed and the inadvertent setting of a packaging condition which could not be met, to amend the Schedule 5 entry to capture ≤ 1% indoxacarb with no packaging condition.

Maldison / malathion – A Member noted that the Schedule 3 entry for maldison had been changed at the October 2006 NDPSC Meeting to malathion for harmonisation, but that other references (in Schedule 4 for organophosphorus compounds and the Schedule 5 and 6 entries for maldison) had inadvertently remained maldison. The Member recommended, and the Committee agreed, that these references be changed to malathion for consistency. The Committee also agreed to cross reference maldison, in the index, to Malathion.

Nicotinic acid – A Member noted that the Schedule 3 entry for nicotinic acid included "dosage preparations" which did not have a defined meaning, nor does it appear to be used for other entries. The Member suggested, and the Committee agreed, that "dosage preparations" should be replaced with "divided preparations" containing 250 mg or less of nicotinic acid "per dosage unit".

Drotecogin / drotrecogin – A Member noted that the current Schedule 4 entry "drotecogin" was inconsistent with the INN spelling "drotrecogin". The Committee agreed to adopt the INN spelling.

Methylandrostanolone – A Member noted, and the Committee agreed, that the Schedule 4 entry for methylandrostanolone should have "#" before it as there was an Appendix D entry for anabolic steroids.

Hydrocortisone – A Member noted that it was the Committee's intention at the February 2007 NDPSC Meeting that the new Schedule 4 entry would capture all veterinary use of hydrocortisone. However, the wording of the new entry only captured use in dogs. The Committee agreed that limiting the veterinary component to dogs was inadvertent and to therefore vary decision 2007/49-13 by deleting the words "in dogs". Subsequent to the June 2007 NDPSC Meeting Members noted that the Schedule 2 and 3 entries for hydrocortisone were not limited to human use. Members therefore also agreed, out-of-session, to amend the wording of the Schedule 2 and 3 entries for hydrocortisone to only capture human use.

OUTCOME

The Committee noted that the South Australian "Appropriate Authority" under Part 1 1.(1) had been updated in the SUSDP 22 consolidation to read:

> (e) in South Australia, the Chief Executive of the Department of Health;

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The Committee agreed to the above editorial amendments to nicotine, indoxacarb, maldison, nicotinic acid, drotecogin and methylandrostanolone. The Committee further agreed to vary its February 2007 hydrocortisone decision (2007/49-13) to capture all veterinary use in Schedule 4 (including an out-of-session decision to amend the Schedule 2 and 3 hydrocortisone entries to only capture human use).

Schedule 2 – Amendment (Variation of Decision 2007/49-13)

HYDROCORTISONE and HYDROCORTISONE ACETATE – Amend entry to read:

HYDROCORTISONE and HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations for human dermal use containing 0.5 per cent or less of hydrocortisone in packs containing 30 g or less of such preparations containing:

> (a) no other therapeutically active substance; or
>
> (b) an antifungal as the only other therapeutically active substance.

Schedule 3 – Amendment

NICOTINIC ACID – Amend entry to read:

NICOTINIC ACID for human therapeutic use in divided preparations containing 250 mg or less of nicotinic acid per dosage unit **except**:

(a) in preparations containing 100 mg or less of nicotinic acid per dosage unit; or

(b) nicotinamide.

Schedule 3 – Amendment (Variation of Decision 2007/49-13)

HYDROCORTISONE and HYDROCORTISONE ACETATE – Amend entry to read:

HYDROCORTISONE and HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations containing 1 per cent or less of hydrocortisone:

(a) for human dermal use, in packs containing 30 g or less of such preparations; and

(i) containing no other therapeutically active substance; or

(ii) containing an antifungal but no other therapeutically active substance; or

(b) for human rectal use, when combined with a local anaesthetic but no other therapeutically active substance **except** unscheduled astringents:

(i) in undivided preparations, in packs of 35 grams or less; or

(ii) in packs containing 12 or less suppositories,

except when included in Schedule 2.

Schedule 4 – Amendments

DROTECOGIN – Amend entry to read:

DROTRECOGIN.

METHYLANDROSTANOLONE – Amend entry to read:

METHYLANDROSTANOLONE.

ORGANOPHOSPHORUS COMPOUNDS – Amend entry to read:

ORGANOPHOSPHORUS COMPOUNDS with anticholinesterase activity for human therapeutic use **except**:

(a) when separately specified in these Schedules; or

(b) preparations containing 2 per cent or less of malathion for external use.

Schedule 4 – Amendment (Variation of Decision 2007/49-13)

HYDROCORTISONE – Amend entry to read:

HYDROCORTISONE:

(a) for human use **except** when included in Schedule 2 or 3; or

(b) for veterinary use.

Schedule 5 –Amendments

INDOXACARB – Amend entry to read:

INDOXACARB (Includes the R and S enantiomers) in preparations containing 1 per cent or less of indoxacarb.

MALDISON – Amend entry to read:

MALATHION in preparations containing 10 per cent or less of malathion **except**:

(a) for human therapeutic use; or

(b) in dust preparations containing 2 per cent or less of malathion.

Schedule 6 – Amendment

MALDISON – Amend entry to read:

MALATHION **except**:

(a) when included in Schedule 5;

(b) for human therapeutic use; or

(c) in dust preparations containing 2 per cent or less of malathion.

Appendix H – delete entry

Nicotine.

20.3 SUSDP AMENDMENT

The Committee noted SUSDP 22 Amendment 1. There were editorial amendments or errata to the Amendment.

22. CLOSURE AND NEXT MEETING

The Chair closed the Meeting at 2.30pm 28 June 2007 and advised that the next scheduled Meeting is 9-11 October 2007. However, he asked Members to give consideration to holding the Meeting on 16-18 October 2007 and to advise the Secretariat.